Frailty: biological risk factors, negative consequences and quality of life

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biological risk factors, negative consequences and quality of life

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Chapter 1

General Introduction

General Introduction

In 2003 the Netherlands had 16.192.572 inhabitants and 13.7 percent was aged 65 and over (http://statline.cbs.nl). In that same year, life expectancy at birth was 76.2 years for men and 80.9 years for women. The population in the Netherlands will continue to grow older. In 2010 it is expected that 15 percent of the population will be aged 65 and over, and this percentage is expected to grow to almost 24 percent in 2040, which is estimated to be over 4 millions of persons aged 65 and over. Life expectancy at birth is also expected to continue to increase in the next thirty-five years to 79.2 years for men and 82.6 years for women. Therefore, an increasing number of people will grow old and they will become slightly older in the next thirty-five years.

Despite an increasing life expectancy, healthy life expectancy (expected years in good health) is increasing in the Netherlands only for men while the trend for women is not clear (1). Women in the Netherlands live on average almost twenty years in suboptimal health and for men this is a period of 14 years (1). In the year 2000, for men the healthy life expectancy was 60.8 years and for women 61.3 years. In the year 2000, of all persons aged 65 and over, 18.1 percent was limited in ADL-functions (activities of daily living, e.g. bathing, dressing) and over 60 percent suffered from one or more chronic conditions. For the aging individual this means that he or she is likely to be confronted with health decline and disability. A concept that is relatively new and developed to describe the multiple problems that older persons frequently experience with aging is frailty.

What is frailty?

Frailty is a fast growing research area in gerontology and geriatric medicine, as a concept to investigate its causes, risk factors and adverse outcomes. Frailty is a term that has not been often used before the past fifteen years (2-5). The concept of frailty has been used as a reservoir for different problems that persons experience with aging. The term frailty has often been used exchangeably with disability and chronic diseases (3;6;7). Another term often used to describe health decline in older persons has been failure to thrive, a concept which originates from pediatrics (8;9). Verdery defined failure to thrive in older people as a syndrome identified as unexplained

weight loss and loss of function, which he states is similar to what other authors have called frailty (8). Another term, used before frailty emerged to describe multiple declines with aging, is the disuse syndrome by Bortz (10). Historically, frailty is a term often used with different definitions; most definitions included the adverse health outcomes of frailty. For example, in 1988 Woodhouse (11) described frail elderly as individuals, aged 65 and over, dependent on others for activities of daily living and suffering from several diseases whereas in 1989 Gillick (12) described frail older persons as “old debilitated individuals who cannot survive without the help from others”.

In 1991, two of the first definitions that used criteria to define frailty were described. Winograd et al. (13) defined frailty as “the presence of one of the following criteria; cerebrovascular accident, chronic and disabling illness, confusion, dependence in ADL’s, depression, falls, impaired mobility, incontinence, malnutrition, polypharmacy, pressure sore, prolonged bed rest, restraints, sensory impairments, socio-economic or family problems. Speechley and Tinetti (14) defined frailty as present when older adults had at least four of the following characteristics: age $\geq$80 years, being depressed, balance and gait problems, rarely or never walk for exercise, use of sedatives, decreased shoulder strength, any lower extremity disability, decreased knee strength, and loss of near vision.

In the more recent definitions, some sort of impaired physiological functioning is included and the adverse outcomes are excluded. For example, in 1992, Buchner and Wagner (15) defined frailty as “the state of reduced physiologic reserve associated with increased susceptibility to disability” (see Figure 1). In 1997 Campbell and Buchner (16) have defined frailty as “a loss of the person’s capability to withstand minor environmental stresses”.

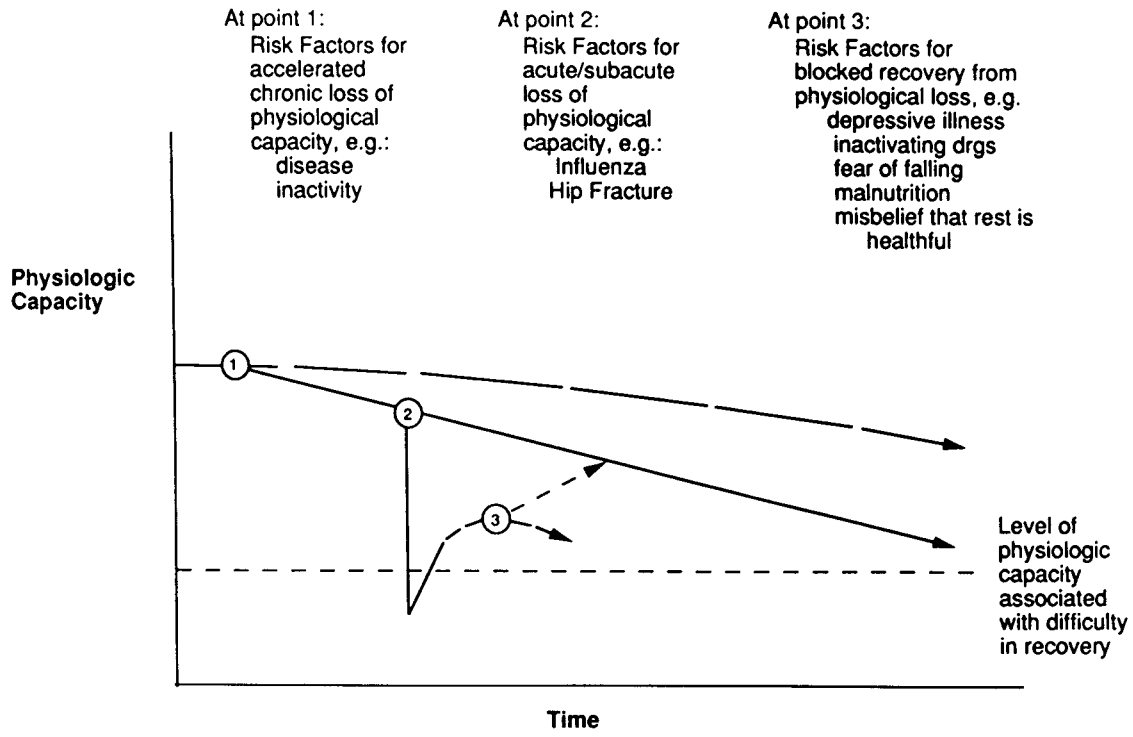

Figure 1. Conceptual model how risk factors cause frailty. Reprinted from Clin. Ger. Med 1992 8(1), 1-17, Buchner & Wagner, Preventing frail Health with permission from Elsevier.

Another example of a definition that includes multisystem decline is described in 1998 by Strawbridge et al. (17) “a syndrome involving deficiencies in two or more domains involving physical, nutritive, cognitive and sensory capabilities”. And a very frequently used definition is that of Fried et al. (18) defined frailty in 2001 as present when three or more of the following criteria were present; shrinking (measured with weight loss), weakness (measured with muscle strength), poor endurance and energy (measured with self-reported exhaustion), slowness (measured with walking speed) and low physical activity.

Recently, the term frailty is used to indicate high risk for adverse outcomes such as falls, disability, institutionalization, and death in older persons (2;7;15;16;18-25). The term is often used in clinical practice and research but there are no widely accepted criteria for frailty yet. Frailty can be seen as a position on a continuum from healthy at one end and slightly frail, moderately frail to very frail at the other (22;24;26) (see Figure 2).

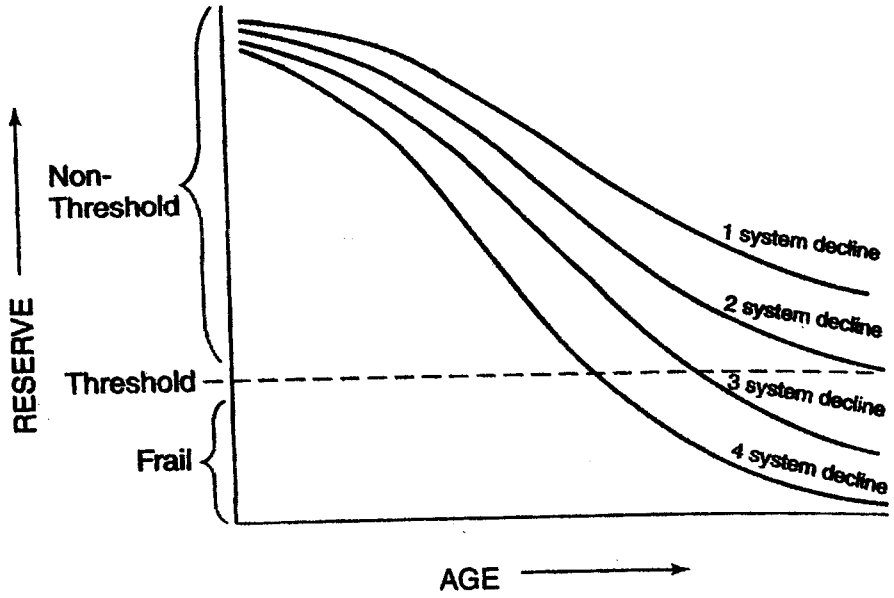

Figure 2. Theoretical figure showing the aggregate effect of declines in function across multiple systems. Reprinted from Principles of Geriatric Medicine and Gerontology, Chapter 116 Frailty and Failure to Thrive, Fried & Walston 2003, 1487-1502, with permission of The McGraw-Hill Companies.

While there is no consensus on the definition yet, there is agreement on the impact of frailty on the older person, their family, and the caregivers as well as on society as a whole (20;27). As the number of older persons increases, the prevalence of frailty is increasing. Frailty will be a major health problem and will lead to an increase in the use of health care by older persons. As no widely accepted definition is agreed upon, current estimates of the number of people with frailty vary. For example, in 1990, the American Medical Association stated that 20% of the adults aged 65 years and over can be considered frail (multiple diseases that functionally limit normal activity), up to more than 40 % of the adults aged 85 and over (28). A study by Fried et al. in which frailty was defined as the presence of three out of five criteria; shrinking/weight loss, weakness, poor endurance and energy, slowness and low physical activity, found a prevalence of 7% (18) in men and women aged 65 years and older using data from the Cardiovascular Health Study. In this study, frailty was more prevalent among women than men. A study of Chin A Paw et al. in which frailty was defined as inacitivty and low energy intake or weight loss or low BMI, found a prevalence 6% in older men aged 65 and over in the Zutphen Study (29).

Because frailty is a potentially reversible state, it is important to develop an instrument for case finding. Recent studies have shown that recovery from disability is most likely to occur in the first months after disability onset while the more frail persons are less likely to improve in functional status (30;31). Interventions such as home visits and comprehensive geriatric assessment have been shown to be effective when administered to older people in the beginning stages of frailty, while those with more advanced frailty benefited less from the interventions (32;33).

The evidence so far seems consistent, but in fact is limited in scope. Firstly, although frailty is conceived as a dynamic state with high risk of adverse outcomes, most investigators used a single moment definition of frailty, i.e. a static definition. In these models, the adverse outcomes are predicted by baseline characteristics in which no deterioration in health is included. However, change in health reflects the definition of frailty that includes an unstable state with high risk for adverse outcomes. In this thesis, a dynamic and a static definition of frailty will be investigated.

Furthermore, frailty, disability and chronic diseases are related but different concepts (19) which are often used together. However, defining all three concepts separately can give more insight in risk factors, treatment and possibly interventions.

A model frequently used to describe the pathway of disability is the disablement process by Verbrugge and Jette (34) (see Figure 3).

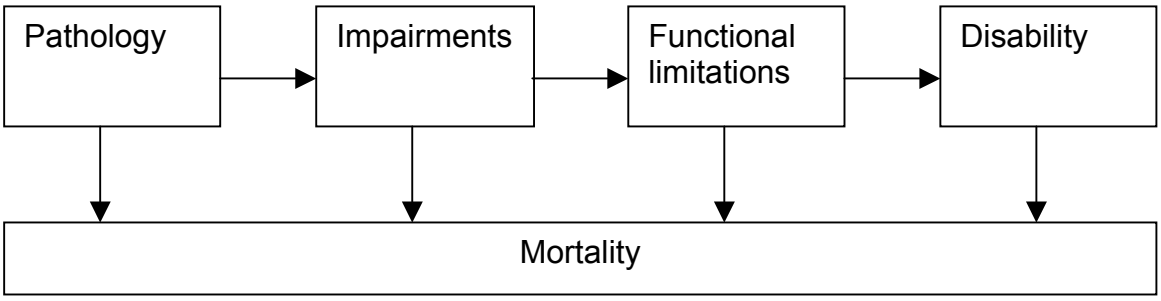

Figure 3. The Disablement process

The disablement process describes the pathway from pathology to disability (34). Pathology includes biochemical and physiological abnormalities that are medically labeled as disease. Impairments include dysfunctions and significant structural abnormalities in specific body systems. Functional limitations include restrictions in performing basic physical and mental activities in daily life such as reaching or stooping, whereas disability is difficulty in performing activities in daily life, such as household activities, job and personal care. The distinction between functional limitations is that functional limitations refer to a person's capability without the situation, while disability refers to functional limitations in a social context.

Verbrugge reported recently that frailty can be seen in the disablement process as a constellation of impairments, a syndrome (35). Frailty can be seen as a precursor state of functional limitations and disability. Disabled persons can become frail when more areas of functioning decline with aging. Frail people can become disabled due to decline in multiple systems, suffering from the adverse outcomes of frailty. Likewise, a person with one chronic disease can be very stable but when the number or severity of chronic diseases even mildly increases, then this person can become frail. In this thesis the relationship between frailty, chronic diseases, disability and adverse outcomes are studied.

Furthermore, two recent reviews stated that so far, research has focused on medical factors and many social and psychological factors have been neglected (2;25). Morley suggested that the severity of frailty can be influenced by social factors such as low income, low education and lack of support (36). Therefore, in this thesis, psychological variables are included in our frailty definition. We also included social variables as confounders in the relationship between frailty and the adverse outcomes.

So far, there is little empirical evidence for the role of endocrine and inflammatory markers and the development of frailty yet. There are many causes of frailty suggested, all of which can interact in a downward spiral of frailty. Recently much research has been done to gain more insight in the biological risk factors of frailty and several mechanisms are described in the literature. Morley et al suggested four factors; sarcopenia, arteriosclerosis, cognitive impairment and malnutrition (36). Sarcopenia is a term used to describe loss of muscle mass and strength with aging, and arteriosclerosis decreases the blood flow to the muscles, aggravating sarcopenia. Cognitive dysfunction leads directly or indirectly to frailty due to

decreased food intake. Bortz described also four causes of frailty: genetics, diseases and injuries, lifestyle and ageing (23). Errors in the genetic program contribute to frailty by muscle, bone or other deformations. Diseases and injuries may provoke frailty. Lifestyle factors such as nutritional problems and inactivity together with aging per se increase muscle weakness that leads to frailty. Another mechanism of frailty is the negative spiral in which inflammation, neuroendocrine deregulation and sarcopenia may play a role (37). This cycle can begin at any point (24;38-43).
A recent model of the pathway of frailty is shown in Figure 4.

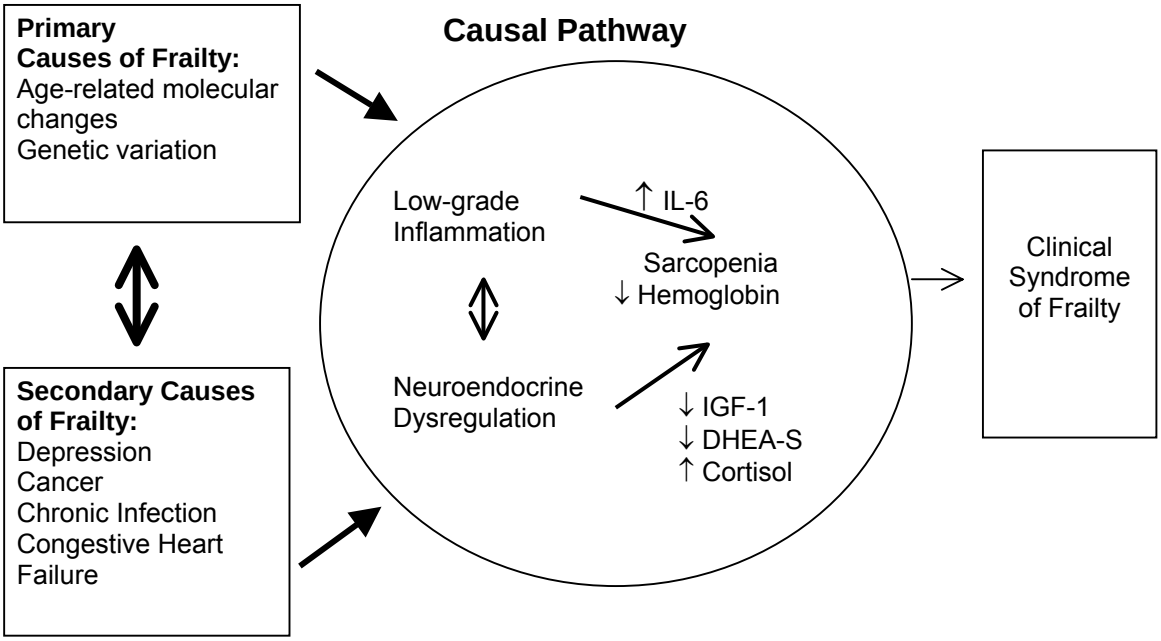

Figure 4. Hypothetical Causal pathways towards frailty. Reprinted from Geriatric Palliative care, Chapter 9 Frailty and its Implications for Care, Walston JD, Fried LP 2003, 93-109. Edited by R.S. Morrison and D.E. Meire with permission from Oxford University Press.
IL-6 interleukin 6, IGF-1= Insuline like growth factor-1, DHEA-s =Dehydroepiandodrosterone sulfate

Inflammation is a response to different stimuli; pathogens, physical trauma and chemicals stimulate monocytes, macrophages and other cells to produce cytokines that induce the inflammation process. Aging is associated with increased release of cytokines and several of those cytokines such as C-reactive protein, and

Interleukin-6 (IL-6) are associated with functional decline and mortality (38;44-50). Interleukin-6 plays an important role in the acute inflammatory response and induces the production of hepatic acute- phase proteins such as C-reactive protein (51). Chronic inflammation is associated with chronic diseases such as cardiovascular diseases, rheumatoid arthritis, diabetes mellitus but also with obesity (52). In adipose tissue, pro-inflammatory cytokines are produced. Inflammation has effect on endocrine system functioning. Chronic elevation of IL-6 has a negative effect on muscle mass and inhibits the production of growth hormone and insulin-like growth factor-1 (IGF-1) (47;53). Growth hormone and IGF-1 play an important role in growth and development and maintenance of muscle mass in old age and IGF-1 serum levels decrease with age.

Another endocrine marker is vitamin D. Vitamin D deficiency is also common in the elderly and has been associated with adverse outcomes of frailty such as falls and hip fractures (54;55). Vitamin D deficiency is associated with sarcopenia and decrease of muscle mass, which may play a role in the pathogenesis of frailty but its direct association with frailty has not been examined (54;56). In this thesis, the effect of some biological risk factors will be examined cross-sectionally and longitudinally.

Surprisingly, no study has investigated the effect of frailty on the outcome quality of life for older adults in the community. Quality of life is defined by the World Health Organization as ”an individual’s perception of their position in life in the context of culture and value systems in which they live and in relation to their goals, expectations, standards and concerns”(57). It is a broad ranging concept affected by the person’s physical health, psychological state, level of independence, social relationships, and their relationships to salient features of their environment. The meaning of quality of life has seldom been investigated in older community-dwelling adults, and is supposed to be negatively affected by frailty. Bowling and Fry suggested that the concept of quality of life and its quantitative measurement stems mostly from experts and not lay views (58;59). Quality of life measures can be used by health care professionals to identify and prioritize problems, facilitate communication, screen for hidden problems, facilitate shared clinical decision making and monitor reaction to treatment (60). This requires knowledge of how best to contribute to maintaining or improving quality of life. In this thesis, the meaning of quality of life to frail and non-frail older community-dwelling adults will be studied. In addition, the meaning of frailty and successful aging to older frail and non-frail

persons are investigated to enhance knowledge about those terms from the perspectives of older persons.

Our definition of frailty

Nine frailty markers (low body weight, low peak expiratory flow, poor cognition, vision and hearing problems, incontinence, low mastery, depressive symptoms and low physical activity) were selected on the basis of literature on previous research on frailty (2;17;18;22;26;29;61-63). The validated model of Fried et al. (18) is often used in studies on frailty and it includes five frailty markers. The five frailty markers are weight loss, exhaustion (measured with 2 items of the CESD), low physical activity, slow walking speed, muscle weakness (low grip strength). In this thesis, a comparable measure of frailty was sought but we also wanted to include psychological frailty markers which have often been neglected (2;25). Psychological resources will influence how people cope with their physical problems. Therefore, nine frailty markers were selected, including psychological frailty markers. The studies of Chin A Paw et al. (26;29) showed that inactivity and weight loss were good criteria for selecting frail people. The study of Strawbridge et al. (17) showed that frail persons reported fewer activities, poorer mental health and lower life satisfaction. Strawbridge et al. (17) defined frailty as involving problems or difficulties in two or more functional domains (physical, nutritive, cognitive as well as sensory). Miles et al. (61) examined incontinence as frailty marker and showed that prevalent incontinence and new-onset incontinence was associated with disability which is an adverse outcome of frailty. The study of Rockwood et al. (63) showed that a frailty scale including ADL-activities, continence and cognitive functioning had a dose-response-relationship with mortality.

First we searched for measurement instruments in the Longitudinal Aging Study Amsterdam (LASA) to find instruments comparable to the five frailty markers of Fried et al. (18). The first frailty marker weight loss could be determined, as body weight was available. The second frailty marker, exhaustion was measured with two items of the Center for Epidemiological Studies-Depression scale that is available in LASA. However, these two items are somatic items (64). We included the total score of the CES-D as a psychological marker of frailty. The third frailty marker, physical activity was available in LASA. The fourth frailty marker, walk time was not included in this study. Walk time increases when frailty increases and we see physical decline

as an adverse outcome of frailty. It was therefore not included. The fifth frailty marker was grip strength as a measure of muscle weakness, which was not available at the baseline of LASA. We included peak expiratory flow as a surrogate marker of muscle weakness. At first follow-up of LASA, grip strength was available and it correlated with peak expiratory flow (Spearman rho=0.55). Furthermore, we have included vision and hearing capacity from the model of frailty developed by Strawbridge et al. (17). Depressive symptoms and mastery were included as psychological frailty markers. Incontinence was selected because of the study of Miles et al. (61) and Rockwood et al. (63). Also poor cognitive functioning was included from the scale of Rockwood et al. (63). However, markers such as ADL-activities were not included as frailty markers because limitations in ADL-activities were considered as an adverse outcome of frailty.

In this thesis, frailty is defined as present when a subject has scores above the cutoff on three or more frailty markers. Frailty is defined in a static and dynamic way. The static definition includes low functioning at one moment (one measurement cycle of LASA) and the dynamic definition is based on the change in the frailty markers between two moments (two measurement cycles from LASA).

Longitudinal Aging Study Amsterdam

For this thesis, data from the Longitudinal Aging Study Amsterdam (LASA) were used. LASA is an ongoing multidisciplinary cohort study on predictors and consequences of changes in physical, cognitive, emotional and social functioning in older people in the Netherlands (65;66). The design of LASA is presented in Figure 5. A random sample of ages 55-85, stratified by age and sex according to expected mortality after five years, was drawn from population registers of eleven municipalities in the west, south and northeast of the Netherlands. The sample was representative of the Dutch older population. The baseline examination of LASA took place in 1992/1993 and 3107 respondents participated. Every three years the participants were interviewed. At each cycle, data were collected in a face-to-face main interview, carried out in the subjects' home or institutional residence, by specially trained interviewers, followed by a medical interview two to six weeks later. The Medical Ethics Committee of the VU University Medical Center approved the study and informed consent was obtained from all respondents.

For this thesis data from the baseline examination (1992/1993), the first follow-up (1995/1996), the second follow-up (1998/1999) and third follow-up (2001/2002) were used. In each chapter of this thesis, a more detailed description of the study sample is provided.

Additional data for the qualitative study were collected in a sample of the LASA respondents. The meaning of quality of life, frailty and successful aging has seldom been investigated in older community-dwelling adults. Therefore, a qualitative study using semi-structured interview was carried out. The aim of this study was to investigate the meaning of quality of life, frailty and successful aging to frail and non-frail respondents. In this study, respondents in Amsterdam and vicinity were included, who participated in the last LASA data collection in 2001/2002 and completed questionnaires in 2004. Respondents with low cognitive functioning in 2001/2002 (with a score below 24 on the Mini Mental State Examination (MMSE) (67)) and institutionalized respondents were excluded for an interview. A theoretical sample was used (68;69) to obtain informants with a varied background which may facilitate maximal information. Respondents had complete data in 2001/2002 on the frailty markers; low BMI, low peak expiratory flow, problems in vision and hearing ability, incontinence, low sense of mastery, depressive symptoms and low physical activity. We selected frail respondents (who have of 3 or more out of the 8 frailty markers mentioned above) as well as respondents without any of the frailty markers.

Objectives

This thesis focuses on frailty and its consequences, possible risk factors for frailty and quality of life in frail and non-frail persons. This thesis on frailty contributes to the literature in that it includes a dynamic and static definition of frailty, it includes physical as well as more psychological frailty markers. It examines several biological risk factors both cross-sectionally and longitudinally. Furthermore, the effect of frailty is studied independently of the effects of chronic diseases and disability. The meaning of quality of life, frailty and successful aging to frail and non-frail older community-dwelling older adults was also studied.

The specific research questions are:

1) What is the relationship between frailty and adverse health outcomes of frailty; physical decline, institutionalization and mortality?
2) What is the association between endocrine and inflammatory makers and incident and prevalent frailty?
3) What is the meaning of quality of life to older frail and non-frail adults and are these important aspects of quality of life different for frail and non-frail older adults?
4) What is the meaning of frailty and successful aging to older frail and non-frail persons?

Outline of this thesis

Chapter 2 describes the relationship between frailty and physical decline. Physical decline is one of the first adverse outcomes of frailty and it is examined in two ways: with an objective measure of physical decline (performance tests) and with a subjective measure of physical decline (the self-reported functional limitations). Frailty is defined in a static and a dynamic way. Additionally, it was investigated whether this effect of frailty was independent of the effect of chronic diseases on physical decline.

Chapter 3 describes the relationship between frailty and the risk of admission to a residential or nursing home. Frailty is suggested to increase the risk of institutionalization but so far this has not often been examined. Frailty is defined in a static and a dynamic way. In addition, it was examined if this relationship was independent of the effect of functional limitations and chronic diseases.

Chapter 4 describes the relationship between frailty and mortality. Furthermore, it was studied whether the risk of mortality is different for men and women since women have a higher risk of becoming frail. Frailty is defined in a static and a dynamic way. Again, it was studied whether the effect of frailty was independent of the effect of functional limitations and chronic diseases.

Chapter 5 describes the relationship between endocrine and inflammatory markers and prevalent and incident frailty. The serum endocrine and inflammatory markers were 25-hydroxyvitamin D, interleukin-6, insulin-like growth factor-1 and C-reactive protein.

Chapter 6 describes the results of the qualitative study on the meaning of quality of life from the perspectives of older people themselves. In this study frail and non-frail respondents were asked to participate, the most important aspects for quality of life were studied, and it was studied if there were differences in what aspects were important for quality of life between frail and non-frail respondents.

Chapter 7 describes the results from the qualitative study on the meaning of frailty and successful aging from the perspectives of older persons themselves. In this study frail and non-frail community-dwelling older men and women were asked to participate and the concept of frailty and successful aging were studied.

Chapter 8 summarizes the main findings of this thesis, discusses the methodology used, and gives recommendations for further research.

The chapters 2 to 7 were written as separate articles for publication in scientific journals, some overlap between the chapters exists in the description of the methodology.

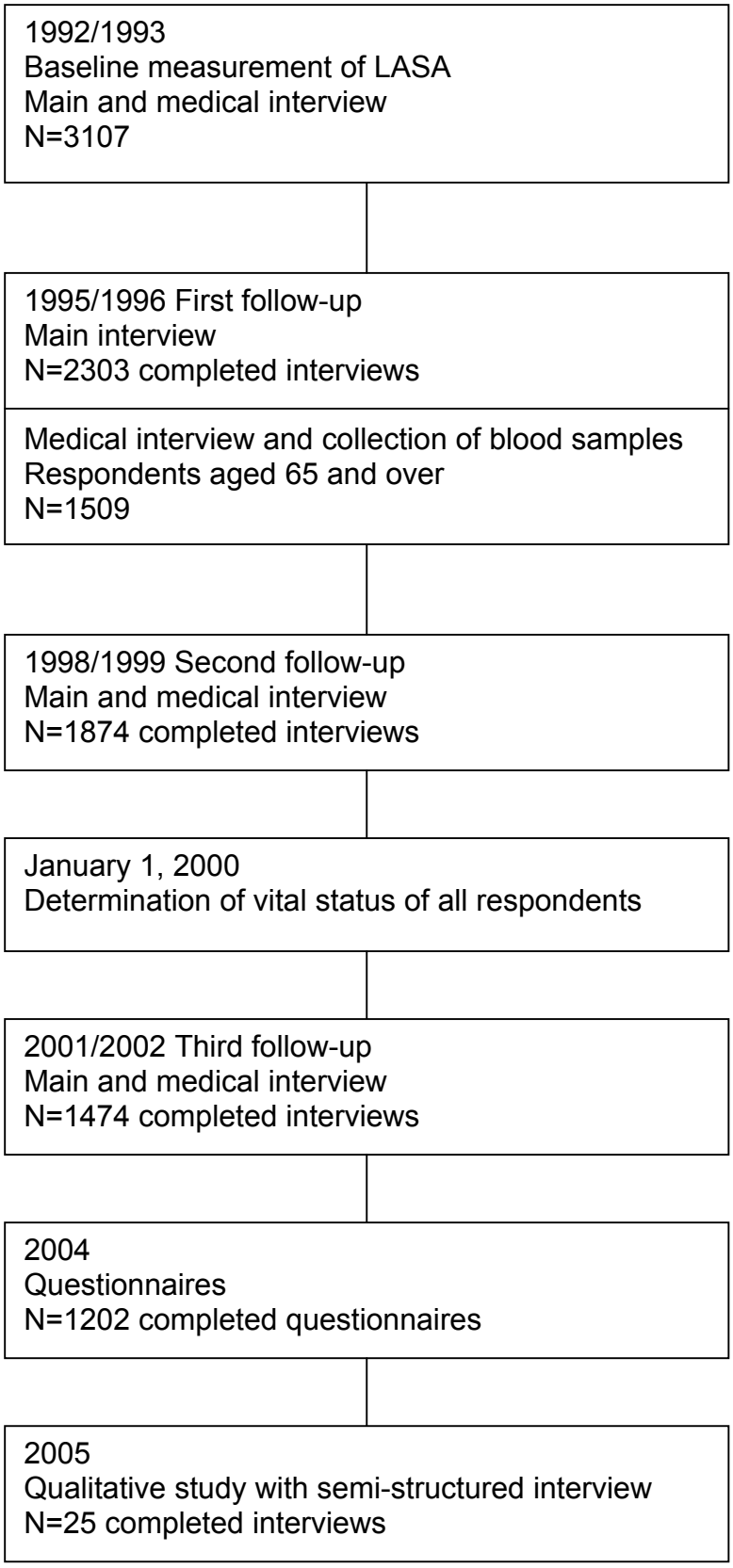

Figure 5. Design of the LASA study.

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Chapter 2

Static and dynamic measures of frailty predicted decline in performance-based and self-reported physical functioning

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Abstract

Objective: To determine the effect of frailty on decline in physical functioning and to examine if chronic diseases modify this effect.

Methods: The study sample was derived from the Longitudinal Aging Study Amsterdam and included respondents with initial ages 65 and over at T_2 (1995/1996) who participated at T_1 (1992/1993) and T_2 and performed physical performance tests (N=1152) or reported functional limitations (N=1321) at T_2 and T_3 (1998/1999). Nine frailty markers were determined in two ways: low functioning at T_2 (static definition); and decline in functioning between T_1 and T_2 (dynamic definition). Using logistic regression analyses, the effect of frailty was examined on change in physical functioning between T_2 and T_3, adjusting for sex, age, education and additionally chronic diseases.

Results: Static frailty was associated with performance decline only in the middle-old group (OR 2.43; 95%CI 1.23-4.80) and associated with decline in self-reported functioning (OR 2.44; 95%CI 1.77-3.36). Dynamic frailty was associated with decline in performance only in women (OR 1.72; 95%CI 1.11-2.67) and with self-reported functional decline (OR 1.77; 95%CI 1.29-2.43). These associations were independent of chronic diseases.

Conclusion: Frailty is more strongly associated with self-reported functional decline in older persons than with performance decline.

Introduction

Frailty is a term often used to describe older persons in a delicate balance being at risk for many adverse outcomes such as falls, disability, institutionalization and death (1-12). There are no widely accepted criteria for frailty. Frailty includes a state of reduced physiologic reserve (3), a diminished ability to carry out the important practical and social activities of daily living (2;12), the presence of chronic diseases (13), and multisystem decline (7-11;14). Some studies defined frailty as the sum of a number of frailty markers (2;3;7-9;14-16).

Most studies so far were not population-based, many were performed in institutions (6;17;18) or used a small sample size (11;19). In the recent population-based study of Fried et al., frailty was established when three or more criteria out of five were present (9). These five criteria were weight loss, exhaustion, low physical activity, walk time and low grip strength (9). This study used limited assessment of only five frailty markers with emphasis on the physiological markers. However, two recent literature reviews concluded that frailty is a multidimensional concept and results from physical, psychological, social and environmental factors, but so far most studies used an uni-dimensional, biomedical perspective (5;20). In the present study both more biomedical and psychological makers of frailty are included.

Frailty, disability and chronic diseases are related but different concepts (21). Disability is difficulty performing a specific ability but can be stable. A frail person is at high risk due to reduced physiological reserves, small changes in health may push them across the threshold of frailty. Fried et al. (9;21) have shown there was an overlap between frailty, disability and chronic diseases. They recommended that the relation between these concepts be examined more closely. A frail person can become disabled if multiple systems decline or as a consequence of one or more chronic diseases. Furthermore, frailty is presumed to be an unsteady state involving a high risk of decline in physical functioning (17). Therefore, it is surprising that empirical studies so far have not examined change in frailty in relation to adverse outcomes.

The outcome measures of frailty studies so far include falls, (ADL-) disability, institutionalization, and mortality. Decline in physical functioning is one of the first adverse outcomes of frailty. In most studies so far, disability was based on self-

reports. Performance-based disability has not been studied in relation to frailty. However, both self-reports and performance tests are valid and reliable measures but measure partly different aspects of physical functioning and therefore can be considered to complement each other (22-24). Performance-based measures of functional status are modestly associated with self-reported measures on a cross-sectional and longitudinal basis (25). Glass suggested that the discrepancies between hypothetical (can you..) and enacted (do you..) may be greater in older people than in younger people (22).

In this study we examined the relation between frailty and physical decline in an older general population sample in the Netherlands. Moreover, we used a static as well as a dynamic definition of frailty and both physiological and psychological frailty markers. The second aim is to study if the relation between frailty and two outcome measures; an objective measure, the performance tests and a subjective measure, self-reported functional limitations, were independent of the effect of chronic diseases.

Methods

Study Sample

The data were collected in the context of the Longitudinal Aging Study Amsterdam (LASA). LASA is an ongoing multidisciplinary study on predictors and consequences of changes in physical, cognitive, emotional and social functioning in older people in the Netherlands. A random sample of ages 55-85, stratified by age and gender according to expected mortality after 5 years, was drawn from population registers of eleven municipalities in three geographical areas in the Netherlands. The sample was representative of the Dutch older population. At each cycle, data were collected in a face-to-face main interview, carried out in the subjects' home or institutional residence, by specially trained interviewers, followed by a medical interview two to six weeks later. The details of the LASA study have been described elsewhere (26-29) (see also http://ssg.scw.vu.nl/lasa/). The Medical Ethics Committee of the VU University Medical Center approved the study and informed consent was obtained from all respondents.

Figure 1. Study Sample

The study sample for the study of functional limitations consisted of subjects who participated in the first follow-up T_2 (1995/1996) and second follow-up T_3 (1998/1999), aged 65 years and older at T_2 and who answered all questions about functional limitations (N=1321) (see Figure 1 for a description of the study sample and design). Of these, 1228 (93.0 percent) had a face-to-face main interview at T_3, 50 persons had a telephone interview (3.8 percent) and for 43 persons a proxy was interviewed (3.3 percent). The sample for the study of the performance tests (which were administered only in the face-to-face main interview) consisted of subjects who completed all performance tests at the first and second follow-up (N=1152). Of the sample in the study of performance test, 43 respondents had missing values on the functional limitation questionnaire, so the sample with data on both outcome measures consists of 1109.

The dropouts from both samples after T_2 were significantly older, had more depressive symptoms, and were more cognitively impaired and more often male ($p<0.05$). The 93 persons who had a telephone or proxy-interview were more cognitively impaired, had more depressive symptoms, were older and had more functional limitations at T_2 ($p<0.05$) than the people who had a face-to-face interview. Moreover, those who declined in performance tests were in better health at T_2 (fewer chronic diseases, better cognition, fewer depressive symptoms) than the respondents who declined in functional limitations.

Measurements

Outcome variables included (1) decline in the overall score on the performance tests and (2) decline in the overall score on the functional limitation scale.

Performance tests

The performance-based tests of physical function included timed measures of walking speed, rising from a chair, putting on and taking off a cardigan and maintaining balance in a tandem stand. The performance tests have been used in several studies and have shown to be a reliable and valid measure of physical functioning (30;31). For the walking test, respondents were asked to walk 3 meters, turn around and walk back the 3 meters as quickly as possible. For the chair stand test, respondents were asked to fold their arms across their chest and to stand up from a sitting position and sit down five times as quickly as possible. For the cardigan

test, respondents were asked to put on and take off the cardigan. For the ability to maintain balance in tandem stand the respondent was asked to put the heel of one foot in front of the other and to stand still as long as possible. After ten seconds the test was stopped. The time for each test was categorized based on quartiles at T_2. The first three tests resulted in a score ranging from 0 (not able/not possible) to 4 (good). The balance test ranged between 0 and 2 (not able, 3-9 seconds, ten seconds). The overall performance was calculated by summing the scores and ranged between 0 and 14.

Self-reported functioning

Functional limitations were assessed by asking the respondent the degree of difficulty they had with six activities of daily living (ADL): climbing stairs, walking 5 minutes outdoors without resting, getting up and sitting down in a chair, dressing and undressing oneself, using own or public transportation, and cutting one's own toenails (32-34). Response categories ranged from (1) "No I cannot" to (5) "Yes without difficulty". The total score was calculated by summing the scores of all activities and ranged between 6 and 30.

Frailty markers

Nine frailty markers were used to study the effect of these markers on physical functioning and were based on previous research on frailty (1;4;9;12;35-38)(See Puts et al., 2005 (1) for an extensive description of our frailty markers). The nine frailty markers were body weight (calibrated bathroom scale), peak expiratory flow (Mini Wright peak flow meter (39), cognitive functioning (MMSE (40)) vision and hearing capacity (asking the respondent are you able to recognize someone's face at a distance of four meters and are you able to follow a conversation with one and four persons, both with aid if needed (41)), incontinence (asking the respondent whether he or she lost urine unintentionally), sense of mastery (short version Pearlin and Schooler Mastery scale (42)), depressive symptoms (CES-D (43)) and physical activity (LASA Physical Activity Questionnaire (44)). We have selected these nine frailty markers because we conceive of the concept of frailty as more than only physical functioning. Several of the frailty markers selected are based on the work of Fried et al. (9) and Chin A Paw et al. (37;38) who studied the effect of weight loss, exhaustion (items from the CES-D) walking time, physical activity and grip strength.

Rockwood et al. (4) and Miles et al. (35) showed the importance of incontinence and cognitive functioning. We have included mastery and depression as the psychological frailty markers (5;20). Strawbridge at al. (11) defined frailty as problems in two out of four (physical, nutritive, cognitive and sensory) and therefore vision and hearing capacity were included.

Covariates

The analyses were adjusted for age, sex, education and total number of chronic diseases. The respondents were asked at baseline the highest level of education achieved. The scores for education ranged from elementary school (low), lower/intermediate general and vocational education (middle), to college and university (high). Seven self-reported chronic diseases were examined: chronic obstructive pulmonary diseases, cardiac disease (myocardial infarction, arrhythmias, congestive heart failure, angina pectoris and narrowing of the coronary arteries), peripheral arterial disease, diabetes mellitus, cerebrovascular accidents, rheumatoid arthritis or osteoarthritis (both conditions were grouped together because respondents appeared to find it hard to differentiate between them) and cancer. These chronic diseases are the most frequent in the Dutch older population with a prevalence of at least five percent. Agreement between respondents' self-reported data and data from the general practitioner has been shown to be satisfactory to good for most diseases studied (29). The number of chronic diseases was calculated by summing all diseases reported by the respondent at T_2.

Cutoffs for the frailty markers

For each of the frailty markers the cutoff distinguishing the frail from the non-frail was determined in two different ways. A static frailty marker was defined as low functioning at T_2 and a dynamic frailty marker was defined as relevant decline in functioning between T_1 and T_2. First, we determined from the distribution of each marker at T_2 the lowest quintile of functioning at that moment for the continuous variables (mastery, peak expiratory flow and physical activity). For the other variables, cutoffs for low functioning were based on the literature (MMSE<24, CES-D$\geq$16, weight BMI<23, any difficulty with vision and hearing, and incontinence).

Second, change in the markers was determined between T_1 (1992/1993) and T_2 (1995/1996). For the continuous variables (CES-D, MMSE, mastery and physical

activities) the Edwards-Nunnally index was used to determine relevant decline. The Edwards-Nunnally index calculates individual significant change based on the reliability of the measurement instrument, the confidence interval and the population mean (45). This index has been developed to determine pretest-posttest recovery. It classifies pre-posttest change as improved or deteriorated using the confidence interval. If the posttest score lies outside of this confidence interval, it is considered to be significantly different from the pretest score. The pre-posttest change is adjusted for regression to the mean. In this study the 90% confidence interval is used for calculating the change in outcome measures and frailty markers.

For decline in peak expiratory flow the criterion of 0.5 standard deviation of the difference was used because the peak expiratory flow measurement is not a scale, and thus reliability analysis is not possible and the Edwards-Nunnally index cannot be calculated. For perception (increasing difficulty with vision and hearing), incontinence (new-onset) and weight loss ($\geq$4.0 kg in 3 year), the cutoff for decline was based on the literature. All independent variables were dichotomized so they can be summed and have a straightforward clinical interpretation. An appendix with all frailty markers and cutoff points is available on request.

Missing values on frailty markers were not imputed. A missing frailty marker was coded as a missing value and counted as not present in the calculation of the total number of frailty markers present. In the study of decline in performance tests 90% of all respondents had complete information about the static frailty markers and 80% had complete information about the dynamic frailty markers. In the study of self-reported decline in functioning 85% of all respondents have complete information on all static frailty markers and 75% had complete information on all dynamic frailty markers.

Frailty

Frailty was defined as present when a subject had scores above the cutoff on three or more frailty markers, which is in accordance with Fried et al.(9). The static definition was based on the frailty markers at T_2. The dynamic definition was based on the change in the frailty markers between T_1 and T_2.

Statistical analyses

Analyses were performed for change in performance tests (N=1152) and change in functional limitations (N=1321) between T_2 (1995/1996) and T_3 (1998/1999). For both outcomes, change was calculated with the Edwards-Nunnally index, see previous section (45). The scores were dichotomized, as decline (1) vs. no decline (0). T-tests and Chi-square tests were performed to assess differences between those who declined and those who did not decline. Subsequently, three analyses were performed.

First, in order to study the associations between each single frailty marker and the outcomes, the association with decline was examined in logistic regression models, adjusting for age, sex and education.

Secondly, to study the relation between both definitions of frailty and both outcomes, four sets of logistic analyses were performed. It was investigated if there were interactions between independent variables. When interaction was present, odds ratios were calculated in the full sample recoding the dummy variables. (46).

Additionally, to study if the association of frailty with physical decline was independent of the effect of chronic diseases we additionally adjusted for the number of chronic diseases. Furthermore, the analyses were adjusted for the other definition of frailty (dynamic when investigating static frailty, and vice versa) to study the unique effect of both definitions of frailty.

Thirdly, in order to study if the risk of frailty of decline increases if the number of frailty markers increases, logistic regression analysis was performed for the number of frailty markers using dummy variables for each count of frailty markers. Persons without frailty markers formed the reference group. Analyses were adjusted for sex, age, education and number of chronic diseases.

Results

Description of frailty

Table 1 presents the characteristics of the study samples. Concerning the outcome decline in performance tests (N=1152), 269 respondents (23.4%) declined in performance tests. Those who declined were older, more often women, less educated, and had more chronic diseases.

For the outcome decline in performance, in men, 59 (11.1% of all men, N=530) were frail in the static sense and 92 (17.4%) frail in the dynamic sense. And in men, 31 (5.8%) were frail in both the static and dynamic sense. In women, 122 women (19.6% of all women, N=622) were frail in a static sense and 123 (19.8%) in a dynamic sense. And in women, 61 (9.8%) were frail in both the static and dynamic sense.

Concerning the outcome decline in self-reported functioning, 331 respondents (25.1%) declined in functioning. Those who declined were older, less educated, had more chronic diseases and had more frailty markers present. In men, 76 (12.9% of all men, N=588) were frail in the static sense and 105 (17.9%) in the dynamic sense. In men, 39 (6.6%) were frail in both the static and the dynamic sense. In women, 153 (20.9% of all women, N=733) were frail in the static sense and 147 (20.1%) frail in the dynamic sense. Eighty women (10.9%) were frail in both the static and dynamic sense.

For all single frailty markers the association with both outcomes adjusting for age, sex and education is shown in Table 2.

Table 1. Characteristics of the study sample

Characteristics	No decline Performance N=883 N (%)	Decline Performance N=269 N (%)	No self-reported decline N=990 N (%)	Self-reported decline N=331 N (%)
Mean age at T_2	74.1 (SD6.1)	77.3 (SD6.4)***	74.2 (SD6.1)	78.3 (SD6.4)***
Sex (% women)	462 (52.3%)	160 (59.5%)*	534 (53.9%)	199 (60.0%)
Performance score T_2 (0-14)	9.0 (SD3.2)	8.4 (SD3.3)*		
Self-reported score T_2 (6-30)			27.7 (SD4.1)	24.3 (SD5.4)***
Low education‡	350 (39.6%)	121 (45.0%)*	388 (39.2%)	171 (51.7%)***
Middle education	397 (45.0%)	123 (45.7%)	462 (46.7%)	120 (36.3%)
High education	136 (15.4%)	25 (9.3%)	140 (14.1%)	40 (12.1%)
Not married/widowed‡	376 (42.6%)	145 (53.9%)***	422 (42.6%)	185 (55.9%)***
Married	507 (57.4%)	124 (46.15)	568 (57.4%)	146 (44.1%)
Mean no. chronic diseases T_2	1.1 (SD1.0)	1.3 (SD1.1)***	1.0 (SD1.0)	1.6 (SD1.2)***
COPD††	112 (12.7%)	39 (14.5%)	120 (12.1%)	67 (20.2%)***
Cardiac disease	211 (23.9%)	74 (27.5%)	220 (22.2%)	108 (32.6%)***
PAD††	78 (8.8%)	35 (13.0%)*	84 (8.5%)	54 (16.3%)***
Diabetes mellitus	52 (5.9%)	33 (12.3%)***	60 (6.1%)	44 (13.3%)***
CVA††	53 (6.0%)	18 (6.7%)	53 (5.4%)	43 (13.0%)***
Rheumatoid disease	407 (46.1%)	140 (52.0%)	452 (45.7%)	193 (58.3%)***
Cancer	94 (10.6%)	35 (13.0%)	107 (10.8%)	52 (15.7%)*
Static Frailty markers				
BMI<23 at T_2	116 (14.1%)	34 (13.8%)	128 (14.2%)	45 (16.0%)
Peak flow <290L/Min at T_2	156 (19.1%)	65 (26.5%)*	157 (17.6%)	104 (36.7%)***
Cognition MMSE<24 at T_2	65 (7.4%)	34 (12.7%)**	78 (7.9%)	57 (17.5%)***
Poor vision at T_2	41 (4.7%)	13 (4.9%)	39 (3.9%)	30 (9.1%)***
Poor hearing at T_2	86 (9.8%)	44 (16.8%)**	104 (10.6%)	49 (15.2%)*
Incontinent at T_2	191 (21.6%)	71 (26.4%)	208 (21.0%)	114 (34.4%)***
Mastery <14 at T_2	158 (18.2%)	67 (25.2%)*	163 (17.0%)	101 (32.4%)***
Depression CES-D $\geq$16 at T_2	112 (12.7%)	45 (16.9%)	114 (11.8%)	77 (24.4%)***
Physical activity <76 min/day T_2	165 (18.8%)	70 (26.1%)**	172 (17.8%)	103 (32.9%)***
Dynamic frailty markers				
Weight loss T_{1-2}	95 (12.2%)	43 (18.7%)*	110 (13.0%)	58 (22.5%)***
Decline peak flow >35L/Min T_{1-2}	270 (34.9%)	74 (32.9%)	265 (31.7%)	107 (41.0%)**
Decline cognition EN-index†T_{1-2}	108 (12.3%)	51 (19.1%)**	118 (12.0%)	82 (25.2%)***
Loss of vision T_{1-2}	93 (10.7%)	44 (17.3%)**	94 (9.8%)	48 (15.4%)**
Loss of hearing T_{1-2}	165 (19.1%)	66 (26.5%)*	190 (19.9%)	82 (27.0%)**
New incontinence T_{1-2}	86 (9.8%)	28 (10.5%)	92 (9.3%)	40 (12.2%)
Decline mastery EN-index† T_{1-2}	119 (14.0%)	50 (19.5%)*	140 (14.9%)	67 (22.3%)**
Decline CES-D EN-index† T_{1-2}	111 (12.7%)	37 (14.0%)	112 (11.7%)	59 (18.8%)**
Decline activity EN-index† T_{1-2}	206 (24.0%)	68 (26.8%)	226 (24.2%)	81 (27.1%)
Static frail	119 (13.5%)	62 (23.0%)***	117 (11.8%)	112 (33.6%)***
Dynamic frail	146 (16.5%)	69 (25.7%)**	151 (15.3%)	101 (30.5%)***
Both static & dynamic frail	60 (6.8%)	32 (23.0%)***	60 (6.1%)	59 (17.8%)***

*P<. 05, **P<. 01, ***P<. 001,

† EN-index is decline operationalized with the Edwards-Nunnally index between T_1-T_2.

†† COPD Chronic Obstructive Pulmonary Disease, PAD Peripheral Arterial disease, CVA Cerebrovascular Accident

‡ P-value overall chi-square test for education and marital status

Table 2. Associations between single frailty markers and decline in physical functioning

	OR (95%CI)†† Decline in performance	OR (95%CI)†† Decline in self-reported functioning
Static Frailty markers T_2		
BMI<23	0.97 (0.63-1.50)	1.08 (0.73-1.60)
Low peak flow	1.06 (0.74-1.52)	
Low peak flow men †		1.38 (0.93-2.05)
Low peak flow women †		3.38 (1.97-5.79)***
MMSE<24	1.31 (0.82-2.09)	1.59 (1.07-2.36)*
Poor vision	0.74 (0.38-1.45)	1.74 (1.03-2.94)*
Poor hearing	1.57 (1.04-2.36)*	1.20 (0.82-1.77)
Incontinence	1.05 (0.75-1.47)	1.58 (1.18-2.12)***
Low mastery	1.27 (0.91-1.79)	2.03 (1.49-2.76)***
Depression	1.21 (0.82-1.79)	2.04 (1.45-2.89)***
Low physical activity	1.52 (1.08-2.14)*	2.04 (1.49-2.80)***
Dynamic Frailty markers T_1-T_2‡		
Weight loss men†	2.03 (1.11-3.70)*	2.05 (1.26-3.33)**
Weight loss women†	0.81 (0.45-1.43)	0.73 (0.38-1.41)
Decline peak flow	0.86 (0.62-1.20)	1.66 (1.22-2.27)**
Decline cognition	1.34 (0.91-1.98)	1.81 (1.28-2.56)**
Loss of vision	1.54 (1.02-2.31)*	1.49 (1.00-2.21)*
Loss of hearing	1.25 (0.88-1.76)	1.15 (0.84-1.59)
New incontinence	0.92 (0.58-1.48)	1.15 (0.76-1.74)
Decline in mastery	1.36 (0.93-1.98)	1.57 (1.11-2.21)*
Increase depressive symptoms		1.59 (1.10-2.31)*
Increase depressive symptoms men†	0.41 (0.15-1.08)	
Increase depressive symptoms women†	1.30 (0.81-2.08)	
Decline in physical activity	1.43 (0.97-2.09)	1.69 (1.18-2.43)**

*P<. 05, **P<. 01, ***P<. 001

† Due to significant interaction between low peak flow and sex, increase in depressive symptoms and sex, and weight loss and sex, these results are reported separately for both sexes.

†† OR (95%CI) Odds Ratio and the 95 percent confidence interval, all analyses are adjusted for age, sex and education.

‡ All frailty markers with change between T_1 and T_2 are corrected for the baseline measurement

Static and dynamic frailty

First, the results of frailty in a static sense are described for both outcomes and subsequently the results of frailty in the dynamic sense for both outcomes. For all analyses below, there was interaction between the number of chronic diseases and age, indicating that in older persons the effect of number of chronic diseases on the risk of physical decline increases. This interaction term was included in the analyses below.

There was a significant interaction between age and static frailty for the outcome decline in performance. Age was divided into tertiles to be able to study the effect of frailty for each age group using dummy variables. Therefore the Odds Ratio (OR) of static definition of frailty is given for all three age groups (see Figure 2A). For the outcome decline in performance, the OR for the young-old group was 2.05 (95% Confidence Interval (CI) 0.87-4.84), for the middle-old group 2.94 (95%CI 1.53-5.64), and for the old-old 0.97 (95%CI 0.60-1.58) when adjusting for sex, age an education. When the number of chronic diseases was added, the OR's changed into 1.82 (0.76-4.37), 2.43 (95%CI 1.23-4.80) and 0.98 (95%CI 0.60-1.58). When additionally adjusted for the presence of dynamic frailty, static frailty was still associated with decline in performance in the middle-old group OR 2.18 (95%CI 1.08-4.40) (see Figure 2A).

For the outcome decline in self-reported functioning there was no interaction between static frailty and age and therefore only one OR is reported (see Figure 2B). The OR was 2.82 (95%CI 2.06-3.87) when adjusting for sex, age and education. When this analysis was additionally adjusted for the number of chronic diseases the OR changed into 2.44 (95%CI 1.77-3.36). When additionally adjusting for the presence of dynamic definition of frailty, the OR slightly decreased to 2.19 (95%CI 1.55-3.09).

The results for the dynamic definition of frailty and its association with both outcomes are shown in Figure 3. There was significant interaction between dynamic frailty and sex for the outcome decline in performance tests. The OR of dynamic frailty for men was 0.97 (95%CI 0.56-1.68) and for women 1.82 (95%CI 1.17-2.81) when adjusting for age and education. When additionally adjusting for the total number of chronic diseases, the OR's decreased, OR men 0.96 (95%CI 0.55-1.67), OR women 1.72 (95%CI 1.11-2.67). When additionally adjusting for the static

definition of frailty, for men the OR changed into 0.91 (95%CI 0.52-1.60) and for women the OR into 1.61 (95%CI 1.02-2.55).

For the outcome decline in self-reported functioning there was no interaction between dynamic frailty and sex. The OR for dynamic frailty was 1.97 (95%CI 1.45-2.68) adjusted for sex, age and education (see Figure 3). Additionally adjusting for the number of chronic diseases resulted in OR 1.77 (95%CI 1.29-2.42). Furthermore the OR when additionally adjusting for the presence of static frailty changed into 1.35 (95%CI 0.96-1.90).

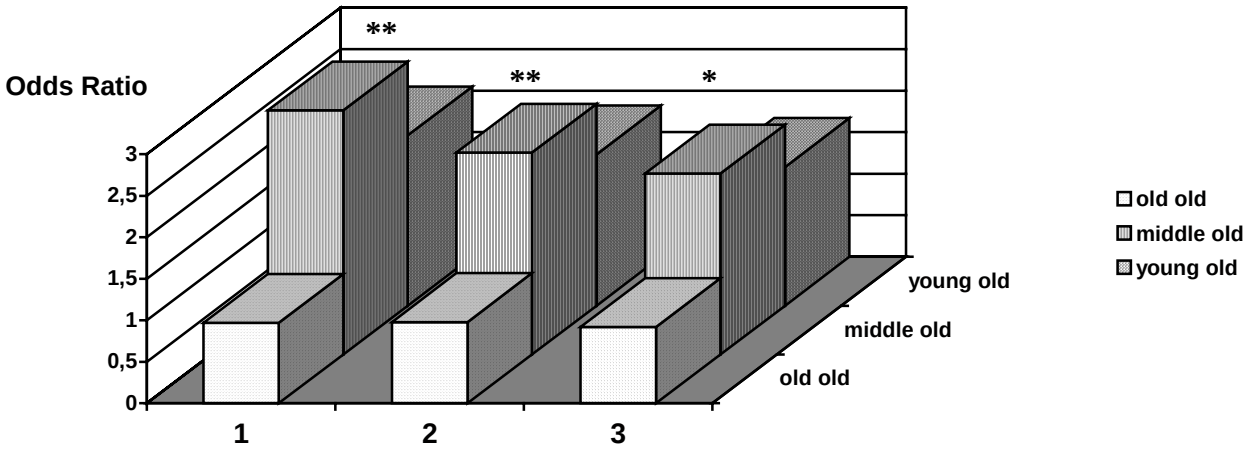
Total number of frailty markers

Logistic regression analyses were performed to compare the effect of the different numbers of frailty markers with the reference group without frailty markers. For the outcome self-reported functional decline, both the static and dynamic definition of frailty, there was an increase in the odds ratio for decline when the number of frailty markers increased (Table 3).

For the outcome decline in performance tests, the association between an increase in the total number of frailty markers and decline was less clear. The total number of static frailty markers shows a small increase. The total number of dynamic frailty markers is presented for men and women separately because of a significant interaction between the number of frailty markers and sex. In men, no association was found and in women, an increased risk with increasing numbers of frailty markers can be seen (Table 3).

All analyses were repeated for persons for whom valid measures of both outcome measures were available (N=1109). This did not change the results (analyses not shown).

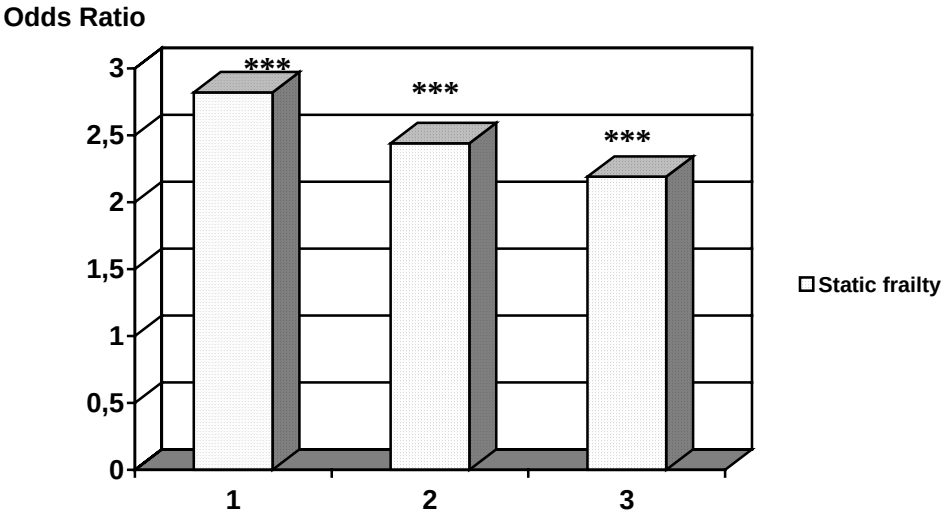
Figure 2. Associations of the static definition of frailty with both outcomes



2a Decline in performance-based functioning

*P<0.05, **P<0.01, ***P<0.001.

1) Adjusted for age, sex and education
2) Adjusted for age, sex, education, and the number of chronic diseases.
3) Adjusted for age, sex, education, the number of chronic diseases and the other definition of frailty (dynamic frailty).



2B Decline in self-reported functioning

*P<0.05, **P<0.01, ***P<0.001.

1) Adjusted for age, sex and education
2) Adjusted for age, sex, education, and the number of chronic diseases.
3) Adjusted for age, sex, education, the number of chronic diseases and the other definition of frailty (dynamic frailty).

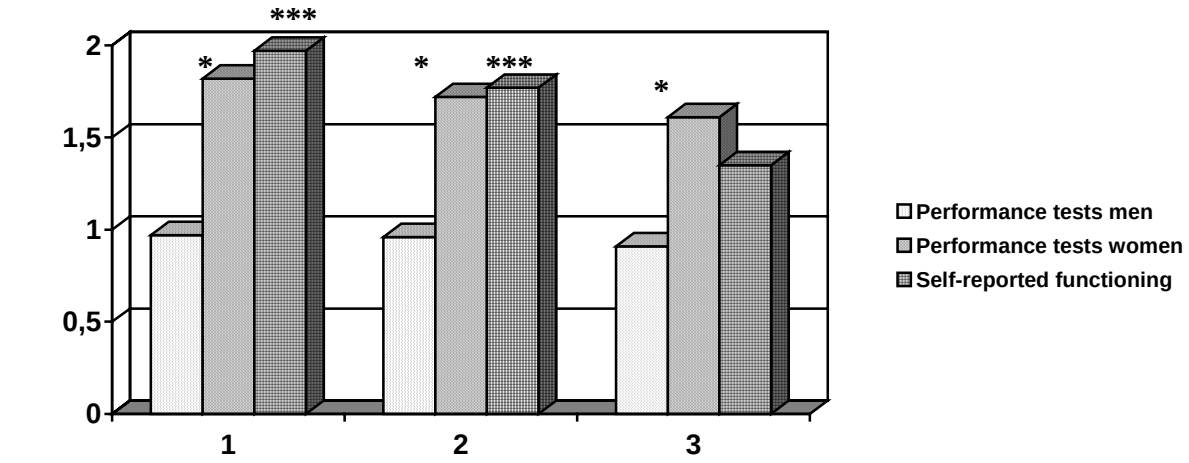


Figure 3. Associations of the dynamic definition of frailty with both outcomes.

*P<0.05, **P<0.01, ***P<0.001.

1) Adjusted for age, sex (only for self-reported functioning) and education
2) Adjusted for age, sex (only for self-reported functioning), education, and the number of chronic diseases.
3) Adjusted for age, sex (only for self-reported functioning), education, the number of chronic diseases and the other definition of frailty (static frailty).

Table 3. Associations between Number of Frailty Markers and physical decline

Number of frailty markers	Static frailty markers OR (95%CI)† Decline in performance	Dynamic frailty markers OR (95%CI)† Decline in performance MEN	Dynamic frailty markers OR (95%CI)† Decline in performance WOMEN	Static frailty markers OR (95%CI)† Decline in self-reported functioning	Dynamic frailty markers OR (95%CI)† Decline in self-reported functioning
0	1	1	1	1	1
1	0.85 (0.58-1.26)	0.66 (0.35-1.24)	1.59 (0.91-2.78)	1.10 (0.74-1.63)	1.30 (0.86-1.98)
2	1.35 (0.90-2.002)	0.98 (0.52-1.85)	1.25 (0.70-2.24)	1.63* (1.08-2.44)	1.99** (1.32-3.01)
3	1.55 (0.92-2.60)	0.86 (0.41-1.82)	2.04* (1.07-3.88)	2.83*** (1.74-4.60)	2.72*** (1.71-4.32)
4 or more††	1.28 (0.71-2.29)	0.67 (0.21-2.09)	2.78* (1.22-6.30)	3.32*** (1.97-5.60)	2.14* (1.16-3.95)

*P<. 05, **P<. 01,***P<. 001.

† OR (95%CI) Odds ratio and the 95 percent confidence interval

†† The respondents with four or more frailty markers were pooled together because of small numbers. Analyses were adjusted for age, sex, education and number of chronic diseases.

Discussion

In this prospective population-based study, a static and a dynamic definition of frailty were investigated for their predictive ability for decline in physical functioning. Other studies so far have used only a static definition of frailty. Moreover, in this study an objective measure (performance tests) and a subjective measure (self-reported functional limitations) were used as measures for physical functioning, because they are assumed to measure different aspects of functioning and to complement each other (22-24).

The results showed that static frailty predicted more strongly decline in self-reported functioning than decline in performance. This effect was independent of the effect of chronic diseases or the presence of dynamic frailty. The dynamic definition of frailty was predictive of decline in self-reported functioning independent of the effect of chronic diseases but not after adjustment for static frailty. Dynamic frailty in women, but not in men, had an effect on decline in performance independent of static frailty.

Our results are consistent with the study of Fried et al. (9) in that frailty is associated with decline in physical functioning. We were able to study the effects of nine frailty markers. The prevalence of frailty was higher in our study due to the definition of frailty as the presence of three or more frailty markers. In our study nine frailty markers were included, artificially increasing the risk for each individual to have three or more markers. Nevertheless, the odds ratio's for decline in this study were comparable to the hazard ratios for worsening mobility and ADL-disability in the study of Fried (9). The studies by Mitnitski et al. (15;16) showed that an increasing number of frailty markers was associated with a higher mortality risk. Correspondingly, in this study the risk for functional decline increased when the number of frailty markers increased.

Our study lends some support to the evidence found by previous studies that the frailty markers low physical activity, decline in physical activity, low cognition, decline in cognition, incontinence, poor vision, and weight loss are important frailty markers (4;9;38). However, except for low physical activity, none of these markers were consistently associated with decline in both self-reported and performance-based physical functioning.

An important contribution of our study is that it includes psychological frailty markers. Recent reviews suggested that so far frailty has been studied from a more biomedical perspective and more psychological aspects should be taken into account (e.g. isolation, social support and engagement, cognitive impairment and depression) (5;20). The frailty markers cognition, mastery and depression were associated in both the static and dynamic sense to decline in self-reported functioning. Psychological resources will have an effect on how frail persons will cope with decline in functioning.

Another contribution of our study is the introduction of dynamic frailty, which includes decline from a certain level of functioning to a lower level of functioning. It is possible that a person is frail in a dynamic sense but not in a static sense, meaning that this person declines from a high level of functioning to a lower one in three or more areas, but not to the lowest level (static frailty), which represents multisystem decline. This person might experience a loss of the precarious balance. The dynamic definition of frailty, however, was not as predictive for functional decline as the static definition as it lost significance when adjusting for the definition of static frailty. A tentative explanation is that persons who decline from a high level of functioning to a lower level still might have the ability to cope with stress, whereas persons at a low level of functioning have passed the threshold of frailty and are at high risk for adverse outcomes.

The nine frailty markers were more predictive for decline measured with self-reported functional limitations than for decline measured with physical performance tests. There may be several explanations for this finding. First, frailty markers other than those included in this study may predict decline measured with performance tests. Second, Glass (22) proposed that self-report questionnaires which ask people what they can do (“hypothetical tense”) do not measure the same as performance tests (“experimental tense”). A third possible explanation why the frailty markers had a smaller effect on decline in performance tests is that the persons who completed the performance tests were a healthier group. The frailty markers may have had no effect on their functioning but would have had an effect in the people who dropped out of this study because of frailty. A fourth possible explanation is that the performance measures may be unstable, influenced by other factors such as effort and transient phenomena such as fatigue, anxiety and short-term acute illnesses.

A limitation of this study is the self-report measures of chronic diseases and some of the frailty markers (e.g. vision and hearing). Agreement between respondents' self-reported chronic diseases and data from the general practitioner has been shown to be satisfactory to good for most diseases (29). However, we have no information on the severity of the chronic diseases, which has been shown for other outcomes such as mortality to be more informative than simple counts of diseases (47). Diagnosis-based measures of comorbidity were shown to have the greatest predictive validity for 1–year mortality when different measures were compared (48). Another possible limitation of our study is the relatively long period of time between the measurement cycles, resulting in loss of the more frail respondents. The period of three years between T_1 and T_2 might be too long for a definition of frailty. Frailty may develop more quickly when people accumulate more health problems on top of the existing ones. Perhaps especially dynamic frailty in men had no effect because the men became frail faster and dropped out of the study.

Similarly, the period of three years between T_2 and T_3 could also be too long for the measurement of outcome variables. Those respondents who survived the three years were in better health than those who were lost to follow up after T_2. Thus, for a substantial number of subjects, adverse outcomes may have been missed. The loss of respondents and the non-response of the more frail persons may have biased our results. However, this is likely to result in an underestimation of our results.

A final limitation is possible misclassification as a result of missing frailty markers, as missing frailty markers were not imputed. In this study frail respondents (three or more frailty markers present) were compared to the non-frail respondents (respondents with 0, 1 or 2 frailty markers present). This might have led to an underestimation of the effect of frailty, because respondents with missing frailty markers might be classified as non-frail where they would be classified as frail with imputation of the missing frailty markers.

The importance of developing an instrument for finding moderately frail people was shown in recent studies. An intervention study among physically frail older persons living at home showed that persons who were moderately frail benefited the most from the intervention and that those with severe frailty had worsening disability over time despite the intervention (49). A meta-analysis found that preventive home visits were effective in persons in relatively good health in particular when the intervention included multiple domains of functioning (36). Our findings suggest that

frailty is indeed multidimensional and older people with problems in three or more areas of functioning are at high risk for adverse outcomes.

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Chapter 3

The effect of frailty on residential/ nursing home admission in the Netherlands independent of chronic diseases and functional limitations

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Abstract

The aim of this study was to determine the effect of frailty on the risk of residential/ nursing home admission independently of chronic diseases and functional limitations. Frailty consists of multisystem decline and is considered to be a consequence of changes in neuromuscular, endocrine and immune system functioning that occur as people age. Frailty is a combination of multiple impairments in functioning that might lead to functional limitations and disability but it is not clear whether frailty has an independent effect on residential/ nursing home admission. Data were used from the Longitudinal Aging Study Amsterdam. The respondents participated at both T_1 (1992/1993) and T_2 (1995/1996), lived independently at T_2, and were aged 65 and over (N=1503). Nine frailty markers were assessed at two cycles (T_1 and T_2). The frailty markers were defined in two ways: low functioning at T_2 (static frailty); and change in functioning between T_1 and T_2 (dynamic frailty). The outcome variable was residential/ nursing home admission between T_2 and T_4 (2001/2002). Cox proportional hazard analyses were used adjusting for chronic diseases, functional limitations, care received, partner status, income, age and sex. Static (RR 1.93, 95%CI 1.36-2.74) and dynamic frailty (RR 1.69, 95%CI 1.19-2.39) were associated with institutionalization in both men and women independently of the effect of chronic diseases and functional limitations. Additional analyses of the total number of both sets of frailty markers present revealed an increased risk of institutionalization when the number increased. In conclusion, frailty is associated with institutionalization, independently of the effect of chronic diseases and functional limitations.

Introduction

Frailty is a term often used to describe a dynamic state of reduced physiologic reserve (1), disability, co-morbidity (2) and multisystem decline (3-5). There are no widely accepted criteria to identify frail persons (6-8). Frailty is considered to be a consequence of changes in neuromuscular, endocrine and immune system functioning (4). Frailty can be seen as a position on a continuum from healthy at one end and slightly frail, moderately frail to very frail at the other (7;9;10). It can lead to adverse outcomes such as institutionalization and mortality. Some studies defined frailty as the sum of a number of frailty markers (1;3-5;11-13).

Frailty, disability and chronic diseases are related to each other but they are different concepts (14). Frailty is a dynamic state in which an older person is at high risk of adverse outcomes due to reduced physiological reserve capacity; small changes in health may push them across the threshold of frailty. Frailty includes decline in multiple systems (for example decline in sensory functioning, cognitive functioning, physical functioning, psychological functioning) (2-5), which occurs as people age (5;15). In the model of the disablement process by Verbrugge and Jette (16), the pathway from pathology to disability is described. Verbrugge reported recently that frailty could be seen in the disablement process as a constellation of impairments, a syndrome that can lead to functional limitations and disability. Functional limitations include restrictions in basic physical and mental actions such as reaching, stooping, whereas disability is difficulty in doing activities in daily life, such as household activities, job and personal care (17). Frailty can be seen as a precursor state of functional limitations and disability. Disabled persons can become frail when more areas of functioning decline with aging. Frail people can become disabled due to decline in multiple systems, suffering from the adverse outcomes of frailty. Likewise, people with one chronic disease can be very stable but when the number or severity of chronic diseases even mildly increases, then people can become frail (14). Another concept concerning disability is subclinical disability which is described when persons do not report having difficulty with ADL activities or physical functioning but have changed their routine (18;19). These changes in functioning can be the result of frailty and eventually cause adverse outcomes such as disability.

As frailty is a precursor state of functional limitations and disability, it is important to study whether frailty has a unique effect. Frailty is a combination of multiple impairments in functioning, which might lead to disability, but it is not clear whether frailty has an independent effect on residential/ nursing home admission.

Frailty has been shown to be correlated with increasing length of hospital stay and nursing home institutionalization in hospitalized patients (20). Rockwood et al. (21) showed a dose-response relation between increasing frailty and increasing risk of subsequent institutionalization in a community sample. Although frailty is assumed to be a dynamic state, most studies so far have used static definitions of frailty (3;4;20-24). No study has to the best of our knowledge investigated the relation between change in frailty and nursing home admission. However, the use of baseline predictors offers little insight into the course of events leading to institutionalization and the effect of deteriorating health status (25;26). A few studies have focused on the effect of change in predictors other than frailty and found that change in care needs (27), such as an deterioration in advanced ADL's and in increase of lower body limitations, (26;28), predicted institutionalization.

Several authors state that relatively few longitudinal data are available on predictors for institutionalization in representative community-based populations (27;29-31). One of those studies with representative longitudinal data was conducted in the USA (29), the other studies were conducted in Finland (30), Canada (27) and Australia (31). Bharucha et al. (29) found that dementia and medical burden were important predictors for institutionalization in the USA. In Canada Tomiak et al. (27) showed that age and specific medial conditions and functional limitations predicted nursing home admission. Nuotio et al. (30) found that age, urge incontinence, depressive symptoms for men only and living alone only for women predicted institutionalization in Finland. Wang et al. (31) found that a range of non-cognitive factors predicted nursing home placement in Australia. In each of these countries, the care system is organized differently and therefore the results cannot be compared easily across countries.

The Netherlands have a high institutionalization rate compared to other countries (32). In 2003 100,799 persons lived in residential homes and 56,699 lived in nursing homes (33), which was 7.1% of all persons aged 65 and older in the Netherlands in 2003 (http://statline.cbs.nl). In the Netherlands, the expenses for long-

term care facilities are covered by the 'Exceptional Medical Expenses Act' (AWBZ) (National insurance) so that long-term care is accessible for all citizens.

Huge costs are associated with residential/nursing home admission. Frailty may be a potentially reversible state and may be prevented or postponed (34). If persons who are frail can be easily identified and treated, institutionalization may be postponed and frail elderly can live longer in the community, which also corresponds to the wishes of older people.

The aim of this study was to investigate the effect of frailty on the risk of residential/ nursing home admission among men and women in the general population in the Netherlands independent of the effect of chronic diseases and functional limitations. We investigated frailty both in a dynamic as well as in a static sense to examine whether static or dynamic frailty increased the risk of institutionalization more and whether these definitions had own unique effects.

Methods

Study sample

The data were collected in the context of the *Longitudinal Aging Study Amsterdam* (LASA). LASA is an ongoing multidisciplinary study of predictors and consequences of changes in physical, emotional, cognitive and social functioning in older people in the Netherlands (see also http://ssg.scw.vu.nl/lasa). A random sample stratified by age and gender according to expected mortality after 5 years, was drawn from population registers of eleven municipalities in three geographical areas in the Netherlands. At each cycle, data were collected in a face-to-face main interview followed by a medical interview two to six weeks later. The details of the LASA study have been described elsewhere (35-38). The Medical Ethical Review Board of the VU University Medical Center approved the study and informed consent was obtained from all respondents.

The sample for this study (see Figure 1) consisted of respondents who participated in the face-to face main baseline interview (1992/1993, T_1, aged 62 and over) and at first follow-up (1995/1996, T_2) and were aged 65 years and older (N=1944). In the Netherlands persons are rarely admitted to a residential/nursing home under the age of 65 and the circumstances and reasons for admission are

likely to be different than admission at old age, therefore all respondents aged younger than 65 were excluded. Respondents were excluded at T_2 if they were already institutionalized (110, 5.7%). Respondents who had no face-to-face main interview (206, 10.6%) were excluded because in a telephone or proxy interview no frailty markers were measured.

If the respondent refused a normal face-to-face main interview at T_3 (1998/1999) or T_4 (2001/2002), the respondent was offered a short telephone interview (48 at T_3, 67 at T_4) and if the respondent was incapable due to cognitive or physical problems, a proxy (38 at T_3, 63 at T_4) was asked some questions about the respondent. In both these interviews, it was asked if the respondent lived in an institution. Respondents were excluded if they refused or were unable to participate (due to physical or cognitive problems) or could not be contacted at T_3 (53, 2.7%), because no information was available on institutionalization. Those who refused at T_4 were kept in the study sample until T_3 (22, 1.1%). One respondent was excluded because the residential status before death was unknown (1, 0.1%). Finally, respondents were excluded if they had no complete data on functional limitations, income, care received or chronic diseases at T_2 (56, 2.9%). Fifteen respondents (0.8%) were excluded from the analyses because they were censored before the first event (institutionalization) happened. The final sample included 1503 respondents (77.3%). As compared to those included, the non-respondents were significantly older, and had lower cognitive functioning, more depressive symptoms and lower sense of mastery (according to the Pearlin & Schooler Mastery scale) at T_2. There were no differences concerning sex or the number of chronic diseases.

For all respondents who participated at T_2, lived independently, and died before the next measurement cycle, it was determined whether this respondent had been admitted to a residential/nursing home before death. For 18 of these respondents the residential status was unknown. The analyses are performed with these 18 respondents classified as non-institutionalized and as institutionalized to investigate whether these respondents influenced the estimates of the risks of institutionalization.

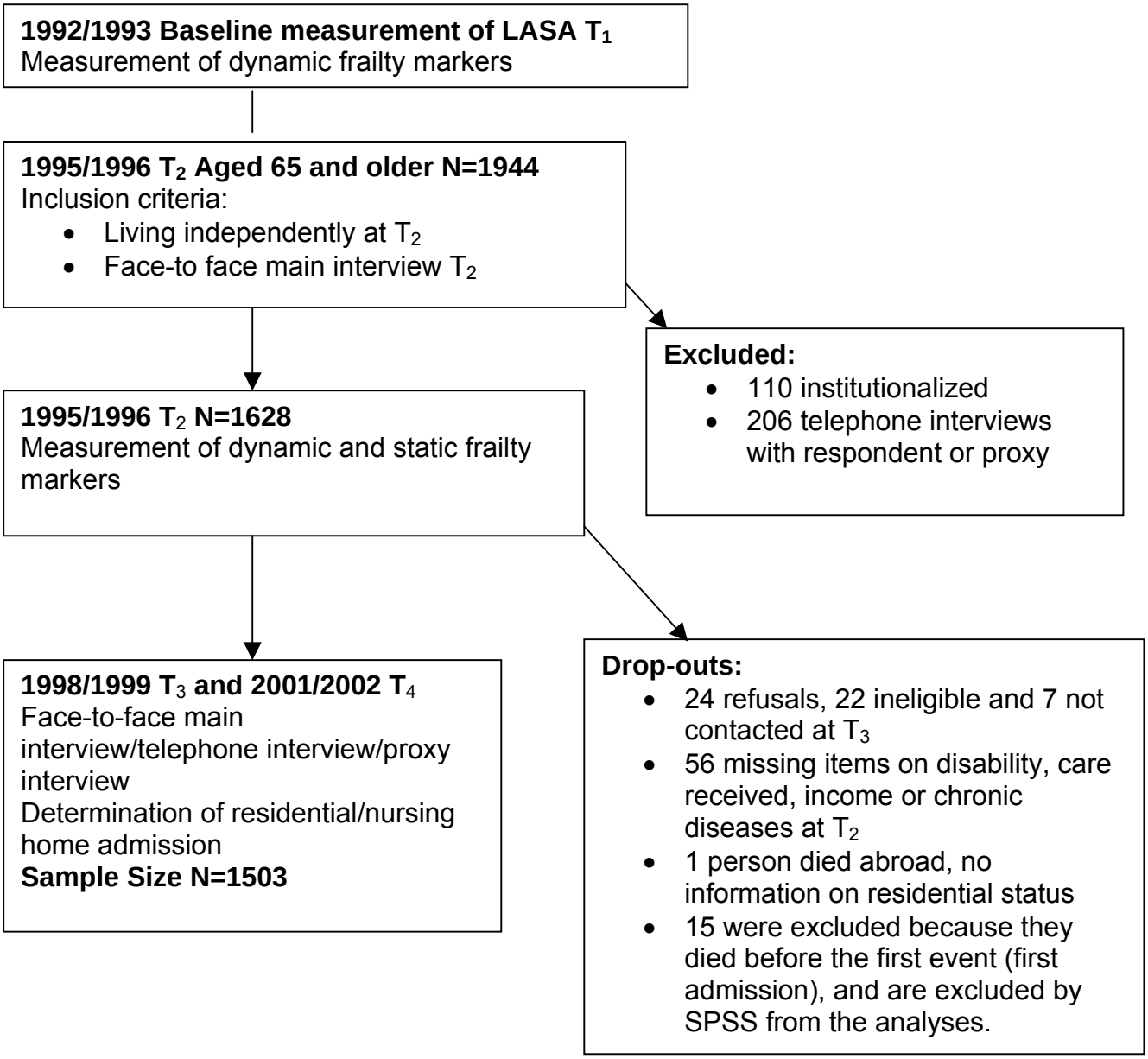

Figure 1. Study participants and dropouts

Measures

Residential/ Nursing home admission

The face-to-face main interview took place at the home of the respondent. The interviewer recorded if this was a residential home or nursing home. With the information about residential status of the respondent at the interviews before, a variable institutionalization (yes/no) was constructed.

Frailty markers

Nine frailty markers were used to study the effect of frailty on residential/nursing home admission (see (11) for an extensive description). The nine frailty markers were body weight (calibrated bathroom scale), peak expiratory flow (Mini Wright peak flow meter (39)), cognition (MMSE (40)), vision and hearing ability (asking the respondent are you able to recognize someone's face at a distance of four meters and are you able to follow a conversation with one and four persons, both with aid if needed (41)), incontinence (asking the respondent whether he or she lost urine unintentionally), sense of mastery (short version of Pearlin and Schooler Mastery scale (42)), depressive symptoms (CES-D (43)) and physical activity (LASA Physical Activity Questionnaire (44)). These nine frailty markers were selected because the concept of frailty was conceived as more than only physical functioning. The frailty markers selected are based on previous studies (2;4;7;9;21;45-47). The validated model of Fried et al. (4) is often used in studies on frailty and it includes five frailty markers. The five frailty markers are weight loss, exhaustion, low physical activity, slowness and weakness. In this study, in addition to a comparable measure of frailty, we also wanted to include psychological frailty markers which have often been neglected (46;48).

In addition, other studies examined the effect of different frailty markers and some of those frailty markers are included as well. The studies of Chin A Paw et al. (49;50) showed that inactivity and weight loss were good criteria for selecting frail people. The study of Strawbridge et al. (2) showed that frail persons reported fewer activities, poorer mental health and lower life satisfaction. Strawbridge et al. (2) defined frailty as involving problems or difficulties in two or more functional domains (physical, nutritive, cognitive as well as sensory). Miles et al. (47) showed that prevalent and new-onset incontinence were associated with disability. The study of Rockwood et al. (21) showed that a frailty scale including ADL-activities, continence

and cognitive functioning had a dose-response-relationship with mortality. First, measurement instruments in the Longitudinal Aging Study Amsterdam (LASA) were selected comparable to the frailty markers of Fried et al. (4). The first frailty marker weight loss could be calculated from body weight. The second frailty marker, exhaustion was measured with two items of the Center for Epidemiological Studies-Depression scale that is available in LASA. However, these two items are somatic items (43). The total score of the CES-D was included as a psychological marker of frailty. The third frailty marker, physical activity was available in LASA. The fourth frailty marker, slowness (walk time) was not included in this study. Walk time increases when frailty increases. Physical decline was used as an adverse outcome of frailty and not as a marker for frailty. The fifth frailty marker was grip strength as a measure of weakness, which was not available at the baseline of LASA. We included peak expiratory flow as a surrogate marker of weakness. At first follow-up of LASA, grip strength was available and correlated with peak expiratory flow (Spearman rho=0.55). Furthermore, vision and hearing capacity were included as suggested by Strawbridge et al. (2). Depressive symptoms and mastery were included as psychological frailty markers. Incontinence was selected because of the study of Miles et al. (47) and Rockwood et al. (21). Also poor cognitive functioning was included from the scale of Rockwood et al. (21). However, markers such as ADL-activities were not included in our frailty markers as they are conceived to be adverse outcomes of frailty.

Cutoffs for the frailty markers

Nine frailty markers were assessed at two cycles, T_1 and T_2. For each of the frailty markers the cutoff distinguishing the frail respondents from the non-frail respondents was determined in two different ways. For the cutoffs for the static frailty markers low functioning at T_2 was used and a dynamic frailty marker was defined as relevant decline in functioning between T_1 and T_2. First, we determined from the distribution of each marker at T_2, the lowest quintile of functioning at that moment for the continuous variables (mastery, peak flow and physical activity). For the other variables (BMI<23, MMSE<24, CES-D$\geq$16, any difficulty with vision and hearing and incontinence) cutoffs for low functioning were based on the literature (2;4;7;9;21;45-47).

Second, change in the markers was determined between T_1 (1992/1993) and T_2 (1995/1996). For the continuous variables, CES-D, MMSE, mastery and physical activities, the Edwards-Nunnally index was used to determine decline (51). The Edwards-Nunnally index calculates individual significant change based on the reliability of the measurement instrument, the confidence interval and the population mean (51). This index has been developed to determine pretest-posttest recovery. It classifies pre-posttest change as improved or deteriorated using the confidence interval. If the posttest score lies outside of this confidence interval it is considered to be significantly different from the pretest score. The pre-posttest change is adjusted for regression to the mean. In this study the 90% confidence interval is used for the independent frailty markers. The scores were dichotomized into decline as (1) vs. no decline (0). For decline in peak flow more than 0.5 standard deviation of the difference was used because reliability analysis of the peak flow measurement is not possible as it is not a scale, and thus the Edwards-Nunnally index cannot be calculated. The other cutoffs were for perception, increasing difficulty with vision and hearing, new-onset incontinence, weight loss $\geq$4.0 kg in 3 year. All independent variables were dichotomized so they can be counted and have a straightforward clinical interpretation (the appendix with all frailty markers and cutoffs is available on request). Missing values on the frailty markers were not imputed.

Frailty

Frailty was defined as present when a subject had scores above the cutoff on three or more frailty markers described above, which is in accordance with Fried et al. (4). The static definition was based on the frailty markers at T_2. The dynamic definition was based on the change in the frailty markers between T_1 and T_2.

Covariates

Age at T_2 was divided into tertiles in this study. The functional limitations score was measured by self-reports at the first follow-up. The respondents were asked about the degree of difficulty they experienced with six activities: climbing stairs, walking 5 minutes outdoors without resting, getting up from and sitting down in a chair, dressing and undressing oneself, using own or public transportation, and cutting one's own toenails (52). Response categories ranged from (1) "No I cannot" to (5) "Yes without difficulty". The total score was calculated by summing the scores. This

score was recoded (6=30), such that an increase in the score reflects an increase in functional limitations. The sum score of functional limitations was divided into tertiles for the analyses.

Seven chronic diseases were asked: chronic obstructive pulmonary diseases, cardiac disease, peripheral arterial disease, diabetes mellitus, cerebrovascular accidents, rheumatoid arthritis or osteoarthritis and cancer. The total number of chronic diseases was used (37).

Household real monthly income was determined by showing a card with 12 possible income categories at T_2. The categories were recoded to the median monthly income and the last category was set at 2614 euros. The household real monthly income of respondents living with a partner was multiplied by 0.7 to make it comparable to respondents who lived alone (53). If the income data was missing at T_2, data of T_1 was used to prevent missing values. Income was divided into tertiles for the analyses.

The care received was determined at T_2. The respondents were asked if they received help with household activities or personal care. If so they were asked from whom they received help. The responses were divided into the categories no care (0), informal care (1), professional care paid out of the pocket (2), and professional subsidized care (3). If respondents had help with both household and personal care from informal and professional caregivers, they were categorized as having professional care.

Partner status was categorized into living with a partner in household at both time points (T_1 and T_2), no partner at both time points, and the loss of the partner between T_1 and T_2, due to death or admission in a care facility.

Statistical analysis

Time to admission was calculated in days from the date of the face-to-face main interview at first follow-up (1995/1996). The design of LASA with three-yearly measurement cycles limits the exact determination of admission date. For the statistical analyses, for all respondents, the date of institutionalization was assumed to be the midpoint between the previous assessment (before the respondent was institutionalized) and the subsequent assessment when the respondent was institutionalized. If the respondent died between two assessments and his last residence was a residential/nursing home, the date of institutionalization was

assumed to be the midpoint between last assessment and death. The respondents were censored at the date of death or the last interview at T_3 or T_4.

The assumption of the Cox proportional hazard analysis, a constant hazard ratio, was checked using LML plots and interaction terms between frailty and time (using different cutoff points of the months of follow-up) in the analyses. The assumption of a constant hazard ratio over time was not violated. The presence of informative censoring was checked by comparing the mean follow-up time of both the frail and the non-frail group that were censored (no event) to each other. It appeared that there was informative censoring, i.e. the mean follow-up duration of the censored people in the frail group was less than for the non-frail group.

The association between frailty and admission to a residential/nursing home was examined in several ways. First, for all single static frailty markers the association with institutionalization was examined using Cox proportional hazard analysis adjusted for age and sex. For all single dynamic frailty markers, the association was also adjusted for baseline values.

In order to examine if frailty predicted institutionalization, Cox regression analysis were performed for the static and dynamic definition of frailty. It was investigated if there was interaction between independent variables and sex. The analyses were adjusted for age, sex, income, partner status, and care received. In a next step, the analyses were additionally adjusted for functional limitations and number of chronic diseases. Subsequently, the analyses were additionally adjusted for the other definition of frailty to study the unique effect of both definitions of frailty (dynamic frailty when investigating static frailty and vice versa).

Thirdly, the association between the total number of frailty markers using both definitions and institutionalization were examined. Dummies were used for each count of frailty markers to study the effect of the different numbers of frailty markers with the reference group, the group with no frailty markers. Respondents with 4 or more markers were pooled together because of small numbers.

As a consequence of the small number of respondents in the youngest age group (the reference category with few respondents institutionalized), the confidence intervals for the other age groups were large. Therefore, we repeated all analyses with the middle tertile of the age group as the reference, excluding the youngest group from the analyses. Finally, we performed sensitivity analyses in which the 18 respondents with unknown residential status classified as not institutionalized in the

main analyses, now were classified as institutionalized. All analyses were carried out using SPSS version 12.0.1.

Results

Table 1 shows the characteristics of the study sample. More women (N=104, 13.1%) than men (N=49, 6.9%) were admitted to a residential/nursing home. Women had more frequently a low income and more often no partner in the household (P<. 05). Women had more static frailty markers than men and had more functional limitations (P <. 05). Respondents who were admitted were older, lived more often alone, had more frailty markers, more chronic diseases and more functional limitations (P <. 05). In particular, those who were institutionalized had more often decline in weight, had more often low peak flow, low cognition, vision problems, were more often incontinent, had more often low mastery, and suffered more often from symptoms of depression (P <. 05) than the non-institutionalized.

Table 1. Characteristics of the study sample

	Male N=712 N (%)	Female N=791 N (%)	Not admitted N=1350 N (%)	Admitted N=153 N (%)
Socio-demographics				
Institutionalized	49 (6.9%)	104 (13.1%)***		
Mean age at T_2 (SD)	75.6 (6.5)	75.3 (6.5)	74.8 (6.4)	80.6 (5.2)***
Low income [a]	184 (25.8%)	352 (44.5%)***	462 (34.2%)	74 (48.4%)**
Middle income [a]	244 (34.3%)	219 (27.7%)	425 (31.5%)	38 (24.8%)
High income [a]	284 (39.9%)	220 (27.8%)	463 (34.3%)	41 (26.8%)
Partner in hh [a,b]	534 (75.0%)	301 (38.1%)***	787 (58.3%)	48 (31.4%)***
No partner in hh a,b T_1 & T_2	144 (20.2%)	418 (52.8%)	472 (35.0%)	90 (58.8%)
Loss of partner a T_1-T_2	34 (4.8%)	72 (9.1%)	91 (6.7%)	15 (9.8%)
No care at T_2 a	343 (48.2%)	398 (50.3%)***	688 (51.0%)	53 (34.6%)***
Informal care at T_2 a	228 (32.0%)	154 (19.5%)	346 (25.6%)	36 (23.5%)
Formal care at T_2 a	52 (7.3%)	82 (10.4%)	104 (7.7%)	30 (19.6%)
Private care at T_2 a	89 (12.5%)	157 (19.8%)	212 (15.7%)	34 (22.2%)
Static frailty markers[e]				
Body Mass Index<23 T_2	101 (15.6%)	111 (16.4%)	186 (15.6%)	26 (20.3%)
Low Peak flow T_2	89 (13.7%)	175 (26.2%)***	228 (19.1%)	36 (28.6%)*
Cognition, MMSE<24 T_2	76 (10.7%)	87 (11.0%)	124 (9.2%)	39 (25.7%)***
Poor vision at T_2	24 (3.4%)	60 (7.6%)***	67 (5.0%)	17 (11.1%)**
Poor hearing at T_2	104 (14.8%)	78 (10.0%)**	161 (12.1%)	21 (14.2%)
Incontinent at T_2	107 (15.0%)	256 (32.4%)***	298 (22.1%)	65 (42.5%)***
Low mastery at T_2	118 (17.1%)	196 (25.8%)***	265 (20.2%)	49 (34.5%)***
Symptoms of depression at T_2	62 (8.9%)	160 (20.7%)***	185 (14.0%)	37 (25.2%)**
Low physical activity (<65 min/day T_2)	194 (28.0%)	87 (11.4%)***	245 (18.6%)	36 (24.8%)
Dynamic frailty markers[e]				
Weight loss T_1-T_2	93 (15.1%)	107 (17.4%)	164 (14.7%)	36 (31.9%)***
Peak flow decline T_1-T_2	249 (40.5%)	192 (31.5%)**	394 (35.4%)	47 (42.0%)
Decline cognition [c]	117 (16.5%)	125 (15.9%)	193 (14.4%)	49 (32.2%)***
Loss of vision T_1-T_2	69 (9.9%)	111 (14.5%)**	153 (11.6%)	27 (18.2%)*
Loss of hearing T_1-T_2	174 (25.1%)	140 (18.6%)**	282 (21.6%)	32 (22.4%)
New incontinence T_1-T_2	64 (9.0%)	86 (10.9%)	129 (9.6%)	21 (13.7%)
Decline mastery [c]	95 (14.1%)	144 (19.4%)**	207 (16.2%)	32 (22.9%)
Increase depressive symptoms [c]	61 (8.8%)	133 (17.3%)***	166 (12.6%)	28 (19.3%)*
Decline physical activity [c]	180 (26.5%)	201 (27.2%)	344 (26.9%)	37 (27.0%)
Frailty				
Static frail	103 (14.5%)	164 (20.7%)**	209 (15.5%)	58 (37.9%)***
Dynamic frail	144 (20.2%)	169 (21.4%)	261 (19.3%)	52 (34.0%)***
Dynamic and static frail	56 (7.9%)	88 (11.1%)*	114 (8.4%)	30 (19.6%)***
Covariates				
Functional limitation score T_2 [d]	8.3 (SD3.9)	10.1 (SD5.1)	9.0 (SD4.4)	12.2 (SD5.7)
Number of chronic diseases at T_2	1.2 (SD1.1)	1.3 (SD1.1)	1.2 (SD1.1)	1.5 (SD1.2)

*P<. 05, **P<. 01, ***P<. 001

[A] p-value overall chi-square test for income, partner status and care received

[b] hh =household.

[c] Decline calculated with the Edwards-Nunnally index.

[d] Score range 6-30, a higher score indicates more functional limitations.

[e] Static frailty refers to low functioning at T_2 and dynamic frailty refers to change in functioning between T_1 and T_2.

Frailty and institutionalization

For all single frailty markers the association with institutionalization was studied adjusting for age and sex (Table 2). Concerning the static frailty markers, low cognition, incontinence, low mastery, and low physical activity were significantly associated with institutionalization. There was an interaction between sex and symptoms of depression. Symptoms of depression were significantly associated with institutionalization in men but not in women.

Table 2. Associations between single frailty markers and institutionalization

	Relative Risk (RR) (95%CI)[c]
Static Frailty markers T_2 [a]	
BMI<23	1.30 (0.84-2.00)
Low peak flow	1.12 (0.75-1.66)
Cognition, MMSE<24	2.53*** (1.74-3.66)
Poor vision	1.62 (0.97-2.72)
Poor hearing	1.12 (0.70-1.78)
Incontinence	1.83*** (1.32-2.54)
Low mastery	1.59* (1.11-2.25)
Symptoms of depression men [d]	3.14** (1.60-6.18)
Symptoms of depression women [d]	1.29 (0.82-2.01)
Low physical activity	1.80** (1.22-2.66)
Dynamic Frailty markers T_1-T_2 [a,b]	
Weight loss	2.13** (1.41-3.20)
Decline peak flow	1.53* (1.04-2.25)
Decline cognition	2.15*** (1.50-3.07)
Loss of vision	1.32 (0.86-2.01)
Loss of hearing	0.88 (0.59-1.32)
New incontinence	1.45 (0.89-2.34)
Decline in mastery	1.36 (0.91-2.02)
Increase depressive symptoms	1.55* (1.02-2.36)
Decline in physical activity	1.71* (1.11-2.65)

*P<. 05, **P<. 01, ***P<. 001

[a] Static frailty refers to low functioning at T_2 and dynamic frailty refers to change in functioning between T_1 and T_2.

[b] All frailty markers with change between T_1 and T_2 are corrected for the baseline measurement.

[c] Adjusted for age and sex.

[d] Due to significant interaction between depression and sex these results are reported separately for both genders

Concerning the dynamic frailty markers, weight loss, decline in peak flow, decline in cognition, decline in physical activity and an increase in depressive symptoms were significantly associated with institutionalization.

In men (N=712), 103 (14.5%) were frail according to the static definition, and 164 (20.7%) in women (N=791). There were 144 (20.2%) men and 169 (21.4%) women who met de criteria for dynamic frailty. In men, 56 (7.9%) fulfilled the criteria for both static and dynamic frailty. In women, 88 (11.1%) met the criteria for both static and dynamic frailty.

Next, Cox's regression analyses were performed to determine whether frailty increased the risk of being institutionalized (Table 3). The Relative Risk (RR) for the static definition of frailty, adjusted for age, sex, income, partner status, care received, number of chronic diseases and the functional limitation score was 1.93 (95%CI 1.36-2.74). The RR for the dynamic definition of frailty was 1.69 (95%CI 1.19-2.39) for both men and women. There was a significant interaction between functional limitations and sex. In women, functional limitations were not associated with institutionalization, but men with the most functional limitations had an increased risk of institutionalization.

Additionally the other definition of frailty was added to the analyses to investigate whether both definitions of frailty had a unique effect. The RR of static frailty adjusted for the presence of dynamic frailty changed into 1.73 (95%CI 1.19-2.50). The RR for dynamic frailty changed into 1.42 (95%CI 0.98-2.06).

The analyses were repeated with the youngest age tertile excluded and the middle age tertile as the reference group. The RR for static frailty was 1.95 (95%CI 1.36-2.80), and the RR for dynamic frailty was 1.79 (95%CI 1.25-2.56) for both men and women. Again significant interaction was found between the functional limitations score and sex. In women, the functional limitation score was not associated with institutionalization. Men with the most functional limitations had an increased risk of institutionalization. Subsequently sensitivity analyses were performed for those 18 respondents for whom residential status was unknown. This did not change the results (results not shown).

Table 3. The association between both definitions of frailty and institutionalization.

	Static frailty [a]	Dynamic frailty [a]
Frailty	1.93*** (1.36-2.74)	1.69** (1.19-2.39)
Sex (0 women, 1 men)	0.50 (0.23-1.07)	0.45* (0.21-0.96)
Age[b]		
Age middle tertile	2.76** (1.46-5.23)	2.90*** (1.53-5.50)
Age old tertile	6.57*** (3.56-12.13)	7.15*** (3.88-13.17)
Income[c]		
Income middle tertile	1.36 (0.90-2.07)	1.34 (0.88-2.04)
Income low tertile	0.97 (0.61-1.54)	0.95 (0.60-1.51)
Care received[d]		
Informal care	1.11 (0.72-1.72)	1.17 (0.76-1.81)
Private care	1.19 (0.74-1.91)	1.24 (0.77-1.97)
Formal care	1.46 (0.90-2.36)	1.52 (0.93-2.46)
Partner status[e]		
No partner in hh T_1 & T_2	1.51* (1.01-2.27)	1.45 (0.97-2.19)
Partner moved out hh between T_1-T_2	1.68 (0.92-3.08)	1.54 (0.86-1.15)
Functional limitations[f]		
Men middle tertile	1.43 (0.60-3.38)	1.37 (0.80-2.23)
Men high tertile	3.29*** (1.56-6.81)	1.93** (1.21-3.07)
Women middle tertile	1.30 (0.69-2.43)	1.09 (0.67-2.35)
Women high tertile	1.27 (0.73-2.22)	1.32 (0.76-2.29)
No. Chronic diseases	1.00 (0.86-1.15)	1.00 (0.86-1.15)

*P<.05, **P<.01, ***P<.001

[a] RR (95%CI) Relative Risk and the (95 percent confidence interval. Both columns of table 3 represent separate analyses for each definition of frailty.

[b] Age, the young tertile is the reference group

[c] Income, the high tertile is the reference group.

[d] Care received, the group with no care is the reference group.

[e] Partner status, hh= household, the group with a partner in the household is the reference group.

[f] Functional limitations, due to interaction between functional limitations and sex the results for functional limitations are shown for both sexes, for both men and women the lowest tertile is the reference group.

The number of frailty markers and the risk of institutionalization

Cox's regression analysis was performed using dummies for each count of frailty markers to study the effect of different numbers of frailty markers based on the static and dynamic definition of frailty. In both men and women the risk of institutionalization increased when the number of static frailty markers increased (Table 4). A similar trend was shown for an increase in dynamic frailty markers but this was less consistent. These results were similar when the youngest age tertile was excluded (results not shown).

Table 4. Associations between Number of Frailty Markers and Institutionalization

Number of frailty markers	Number of static frailty markers RR (95%CI) [a]	Number of dynamic frailty markers RR (95%CI) [a]
0	1	1
1	1.24 (0.72-2.15)	1.50 (0.84-2.69)
2	1.71 (0.98-2.97)	1.67 (0.93-2.98)
3	2.52** (1.41-4.51)	2.48** (1.36-4.54)
4 or more	2.74** (1.47-5.11)	2.42* (1.19-4.93)

*P<. 05, **P<. 01.
[a] RR (95%CI) Relative Risk and the 95 percent confidence interval
Analyses were adjusted for age, income, sex, functional limitations, number of chronic diseases, care received and partner status. (Results for these covariates are not substantially different from those in Table 3).

Discussion

In this prospective study, the influence of frailty on admission to a residential/ nursing home was investigated in a representative population-based study. Moreover, the effects of a static and dynamic definition of frailty were investigated whereas other studies so far have used a static definition of frailty only (4;21;23). In this study we found that static and dynamic frailty increased the risk of institutionalization independently of the effect of functional limitations and the number of chronic diseases. Moreover, the static definition of frailty had a unique effect independently of the dynamic definition of frailty. Furthermore, this study included both physical and

psychological measures of frailty whereas most studies used only physical frailty markers. Each of the psychological frailty markers increased the risk of admission.

The women in this study had more often more functional limitations than men, fulfilled the criteria for frailty more often and had more frailty markers present. However, there was a significant interaction between functional limitations and sex, showing an increased risk of the most impaired men for institutionalization. In women functional limitations had no effect on the risk of institutionalization. Men more often than women still had a partner in the household and received more informal care, whereas women received more professional care. Women also more frequently lost their partner. It seems that men were admitted to a nursing home with less severe health problems than women. It is possible that women have better learned to take care of themselves and others and to arrange care at home, and are therefore more inventive in creating solutions for health problems that enable them to stay at home.

Our results should be compared to studies in other countries with caution. The health care system in the Netherlands differs from that of other countries, e.g. in that the decision to institutionalize is related to the availability of other community services for the elderly. In the Netherlands older persons are often admitted after hospital admission to recover and rehabilitate before they go home (32). In this study, however, all respondents admitted were still institutionalized at follow-up. With these caveats, our study supports evidence from previous studies in several ways. First, we found a risk of institutionalization for frailty similar to that found by Rockwood et al. (21) in Canada. Tomiak et al. (27) found for Canada that after old age, medical conditions and functional limitations were the best predictors of nursing home admission. However, in our study, functional limitations were predictive only for men, not women, and the total number of chronic diseases was not associated with institutionalization. Bharucha et al. (29) found for the USA that the most important risk factor for institutionalization was dementia. In our study no diagnosis of dementia is available but the frailty marker low cognitive functioning increased the risk of institutionalization. Furthermore, in the study by Nuotio et al. (30) in Finland, living alone was found to increase the risk of institutionalization for women and not in men, and in their study more women then men lived alone. In our study, respondents who had no partner in the household or who lost their partner, which were more frequently women, had an increased risk for institutionalization. In the study by Nuotio et al. (30) also in men, incontinence predicted institutionalization which is also in accordance

with our study. Moreover, this study confirms the importance of inactivity, incontinence, and weight loss as frailty markers predictive of institutionalization (2;4;21;45;47).

This study contributes to the literature in that it includes psychological frailty markers. Two recent reviews concluded that more psychological and social factors should be included in future research (46;48). In this study low mastery in men and women, depression in men and for both genders an increase in depressive symptoms increased the risk of admission. An important part of the definition of frailty is the high risk of adverse outcomes due to a precarious balance. Psychological resources will influence how people cope with their physical problems.

The dynamic definition of frailty is another important contribution to the measurement of frailty. Few studies have examined changes in health status (25;26;28;54). It is possible to be frail in a dynamic but not static sense meaning that people decline from a high level of functioning to a lower level of functioning but not to a very low level of functioning (static frail). A person who declines from a high level of functioning to a lower level of functioning but not the lowest is defined as frail only if he or she declines in three or more areas, which represents multisystem decline. This person might experience a loss in reserve capacity threatening the homeostatic balance. In this study those only frail in the dynamic sense, were in better health than those frail in a static sense. However, respondents who fulfilled criteria for both definitions of frailty (static and dynamic frailty), which means that these persons functioned poorly at first follow-up and had experienced decline in functioning between the baseline and first follow-up, had the most health problems. It seems that dynamic frailty has an effect additionally on frailty in a static sense.

Not only health status predicts nursing home admission but also the availability and relation with an informal caregiver. Gaugler et al. (25) suggested that those who experience change or decline in health or function while at home may pose greater challenges to caregivers than those who remain stable over time. In a Dutch study of 15 Municipal Committees on Need Assessment (RIO), the request for institutionalization was frequently done by the relatives of the older person (24). In this study we have no information on who requested the admission. However, it would be interesting to investigate if frail persons themselves ask for admission or if their relatives ask for admission.

The importance of developing an instrument for finding moderately frail people was shown in recent studies. An intervention study among physically frail older persons living at home showed that persons who were moderately frail benefited the most from the intervention and that those with severe frailty had worsening disability over time despite the intervention (55).

A limitation of our study is that we have not examined the effect of combinations of frailty markers. It is possible that certain combinations increase the risk of institutionalization more than other combinations. The most frequent combination of the static frailty markers consisted of incontinence, low mastery and depression, and for the dynamic frailty markers the most frequent combination consisted of decline in peak flow, decline in cognition and decline in physical activity. However, the number of respondents in each combination was very low (N=57 and 19). Future studies should study the effect of specific combinations of frailty markers in larger samples. Another limitation is the non-response and exclusion of subjects lost to follow-up or because of missing values on questionnaires. The non-respondents and those lost to follow-up were older and more often cognitively impaired than those included. These subjects are more likely to be institutionalized. This may have biased our results, most likely resulting in an underestimation of the risk for institutionalization. Furthermore, some of the frailty markers were self-reports (incontinence, perception and physical activity). This might have biased the results too. A limitation is the lack of a more precise date of institutionalization, and therefore less precise estimates. A final limitation was the presence of informative censoring; i.e. the mean follow-up duration of the censored people in the frail group was less than for the non-frail group. Most likely, this informative censoring has underestimated the increased risk of frailty of institutionalization.

Despite its limitations, this study shows that both static and dynamic frailty were a predictor of institutionalization for both men and women, even when adjusting for functional limitations and chronic diseases.

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Chapter 4

Sex differences in the risk of frailty for mortality independent of disability and chronic diseases

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Abstract

Objectives: To determine the effect of static and dynamic frailty on mortality in older men and women.

Methods: A prospective population-based cohort study with three 3-yearly measurement-cycles. The sample was derived from the Longitudinal Aging Study Amsterdam and consisted of respondents who participated in both T_1 (1992/1993) and T_2 (1995/1996) and had complete data on disability and chronic diseases (N=2257). Nine frailty markers were assessed at two cycles (T_1 and T_2). The frailty markers were defined in two ways: low functioning at T_2 (static frailty); and change in functioning between T_1 and T_2 (dynamic frailty). Survival time, calculated in days from T_2 to January 1, 2000, was used as the outcome variable. The predictive ability was examined using Cox proportional hazard analyses separately for men and women.

Results: Women were frailer than men. Static frailty was significantly associated with mortality in men (RR=2.4) and in women (RR=2.6). Dynamic frailty was also associated with mortality in women (RR=2.6) but it was not significantly associated with mortality in men (RR=1.3). When disability and chronic diseases were included in the model as possible mediators, these RR's dropped to 1.6, 2.0, 2.1 and 1.2 respectively, of which the first three were still significant.

Conclusion: Frailty was associated with mortality to a greater extent in women than in men and this effect was independent of disability and chronic diseases. In men, the static definition of frailty was more predictive of mortality than the dynamic definition.

Introduction

Frailty is a term often used to describe older persons in a delicate balance being at risk for many adverse outcomes such as falls, disability, institutionalization and death (1-8). It includes a dynamic state of reduced physiologic reserve (2), a diminished ability to carry out the important practical and social activities of daily living (9;10), comorbidity (11) and multisystem decline (5;6;8). Frailty is considered to be a consequence of changes in neuromuscular, endocrine and immune system functioning (12). There are no widely accepted criteria to identify frail persons (7;10;13). Most authors defined frailty as the sum of a number of frailty markers (1;2;4-6;8). Frailty can be seen as a position on a continuum from healthy through very frail (10;14;15).

Using a rapid clinical screening instrument, Winograd et al. (16) found that frailty was correlated with increasing length of hospital stay, nursing home institutionalization and mortality in hospitalized patients. Mitnitski et al. (17) showed that a frailty index consisting of 20 possible frailty markers was a predictor of mortality in a screened clinical sample aged 65 years and older in Canada. Using a frailty scale, Rockwood et al.(3) showed a dose-response relation between increasing frailty and subsequent institutionalization and death in a community sample. The other study in the general population so far showed that frailty was predictive of falls, ADL-disability and death (8).

The evidence so far seems consistent, but in fact is limited in scope. First, although frailty is conceived as a dynamic state, most studies used static measures of frailty (3;5;8;16-18). As Wolinsky et al. (19) noted, the effect of deterioration in health status has not frequently been investigated. No study so far has used a dynamic measure of frailty for its predictive ability for mortality. Second, two recent literature reviews concluded that frailty is a multidimensional concept and results from physical, psychological, social and environmental factors. However, most studies so far used an uni-dimensional, biomedical perspective (20;21). Although the effect of the number of frailty markers on mortality has been studied, the effect of physical and psychological frailty markers has not been frequently examined.

Third, there are multiple pathways to mortality involving frailty, chronic diseases and disability. Frailty has been shown to predict disability (8). Fried et al.

have shown that not everybody with frailty is disabled, but that both frailty and disability predict mortality (8). The relationship between frailty, chronic diseases and disability should be examined more closely.

Fourth, several explanations have offered as to why frailty affects more women than men (6), but no study has examined sex differences in the association between frailty and mortality. Only differences in prevalence of frailty have been reported (8;9;22) although one study found no sex differences in the prevalence of frailty (11).

The aim of this study was to investigate the effect of frailty on mortality in men and women in the general population in the Netherlands independent of the effect of chronic diseases and disability. Frailty markers were examined using a static and a dynamic definition of frailty and included both physical and psychological markers. Frailty was defined as present when a subject had scores above the cutoff on three or more frailty markers (8). The research questions were:

1) Do static and dynamic measures of frailty predict mortality in a general population sample in the Netherlands?
2) Does the predictive ability of frailty for mortality differ between sexes?
3) Is the predictive effect of frailty on mortality independent of disability and chronic diseases?

Methods

Study sample

The data were collected in the context of the Longitudinal Aging Study Amsterdam (LASA). LASA is an ongoing multidisciplinary study of predictors and consequences of changes in physical, emotional, cognitive and social functioning in older people in the Netherlands. A random sample stratified by age and sex according to expected mortality after 5 years, was drawn from population registers of eleven municipalities in three geographical areas in the Netherlands. At each cycle, data were collected in a face-to-face main interview followed by a medical interview two to six weeks later. The details of the LASA study have been described elsewhere (23;24). The Medical Ethical Review Board of the VU University Medical Center approved the study and informed consent was obtained from all respondents.

A total of 3107 respondents completed the baseline interview. The sample for this study consisted of 2257 respondents (72.6%) who participated in the baseline interview (T_1) and first follow-up interview (T_2) and who answered all questions about functional limitations and chronic diseases. Loss to follow-up after baseline was due to death (13.4%), refusals (2.9%), and inability to participate due to cognitive or physical impairments (1.2%). Furthermore, respondents could not be contacted (0.5%). Excluded were those with a telephone interview (5.3%) and those whose proxies were interviewed (2.5%), and those with missing items on the functional limitations questionnaire (1.3%) or chronic diseases (0.2%). Those lost to follow-up were more likely to be male, unmarried, and older, to have more chronic diseases, more depressive symptoms and to be cognitively impaired. In this study, data were used from both the main interview and the medical interview.

Measures

Mortality

Vital status was traced through the registers of the municipalities in which the respondents were living. Ascertainment was 100 percent complete. For all deaths between the baseline interview and January 1, 2000, date of death was recorded. Mortality after the first follow-up and before January 1, 2000 was used as the outcome variable. Survival time was calculated in days from the date of the interview at first follow-up to 1 January 2000.

Frailty markers

Nine frailty markers (body weight, peak flow, cognition, vision and hearing problems, incontinence, mastery, depressive symptoms and physical activity) were selected on the basis of literature on previous research on frailty and on predictors of mortality (3;8;10;11;14;21;25-27). We haven selected these nine frailty markers because the concept of frailty was conceived as more than only physical functioning. Two recent reviews stated that research has focused on more medical factors and the more social and psychological factors have been neglected (20;21). Several of the frailty markers selected are based on previous work of Fried et al. (8), who examined the effect of five frailty markers (weight loss, exhaustion (measured with two items of the CES-D), physical activity, walk time, grip strength). Also the studies of Chin A Paw et

al. (14;25) showed that inactivity and weight loss were good criteria for selecting frail people.

Instead of the two exhaustion items of the CES-D, we used the total scale score as a measure of frailty to reflect the view that frailty also includes psychological markers. The exhaustion items that Fried et al used are somatic items of the CES-D (8). The study by Strawbridge et al. (11) showed that frail persons reported fewer activities, poorer mental health and lower life satisfaction. The CES-D and sense of mastery were included in the current study.

In the LASA study, grip strength was not available at baseline measurement but was included in the study from the first follow-up measurement. For reasons of consistency, it was desired to study the effect of the same frailty markers in a static and in a dynamic way because frailty is assumed to be a dynamic state with high risk of adverse outcomes. We have selected the peak expiratory flow measure as a proxy of muscle strength. Peak flow and grip strength are correlated (Spearman rho=0.556) in the sample.

Incontinence was selected because Miles et al. (26) introduced it as a frailty marker and showed that prevalent incontinence and new-onset incontinence was associated with disability. Also the study by Rockwood et al. (3), showed that a frailty scale including ADL-activities, continence and cognitive functioning had a dose-response relationship with mortality.

The study by Strawbridge et al. (11) defined frailty as involving problems or difficulties in two or more of four functional domains: physical, nutritive, cognitive as well as sensory, so vision and hearing capacity were included in the current study.

Body weight was measured to the nearest 0.1 kg using a calibrated bathroom scale. Current height was measured using a stadiometer. The Body Mass Index (BMI) was calculated. Peak expiratory flow was measured using a mini-Wright peak flow meter. The respondent was asked to expire three times and the best reading was used (28). Cognitive functioning was measured with the Mini Mental State Examination (MMSE) (29); range 0-30, higher scores indicating better cognitive functioning. A score below 24 points is often used to indicate impaired cognitive functioning. Poor distant vision and hearing problems were ascertained by asking whether the respondent could recognize someone’s face at a distance of four meters (with glasses or contact lenses if needed) and whether they could follow a conversation with one person and a conversation in a group of four persons (with

hearing aid if needed) (30). To ascertain whether respondents were incontinent, they were asked whether they at times unintentionally lost urine (26). Sense of mastery, the extent to which a person has the feeling of being in control of his or her own life, was assessed by using a short version of the Pearlin and Schooler Mastery scale (5 statements) range 5-25, higher score indicating more mastery (31). Depressive symptoms were measured with the Center for Epidemiologic Studies Depression Scale (CES-D) (32) which is a 20-item self-report scale ranging from 0-60, with a higher score indicating more depressive symptoms. It has been shown to be a valid and reliable instrument in older populations. A score of 16 or greater has generally been used to indicate clinically relevant depressive syndromes. To assess the level of physical activity, respondents were asked how often and for how long in the two weeks prior to the interview they had been walking, bicycling, had performed light and heavy household activities and sport activities (33). The total time spent on physical activity was calculated by multiplying the frequency by the duration of each activity, divided by 14. Body weight and peak expiratory flow was measured in the medical interview. At T_2, only persons above 65 were selected for the medical interview.

Cutoffs for the frailty markers

Nine frailty markers were assessed at two cycles, T_1 and T_2. For each of the frailty markers the cutoff distinguishing the frail respondents from the non-frail respondents was determined in two different ways. First, the lowest quintile of functioning at T_2 was determined from the distribution of each marker at that moment for the continuous variables (mastery, peak flow and physical activity). The quintiles were not sex-specific. For the variables MMSE, CES-D, perception, and incontinence, cutoff points for frailty were based on literature (3;8;10;11;14;21;25-27). For low body weight, the body mass index (BMI) was used.

Second, the change in the markers was determined between T_1 (1992/1993) and T_2 (1995/1996). For the continuous variables (CES-D, MMSE, mastery and physical activities), the Edwards-Nunnally index was used to determine decline (34). The Edwards-Nunnally index calculates individual significant change based on the reliability of the measurement instrument, the confidence interval and the population mean (34). This index has been developed to determine pretest-posttest recovery. It classifies pre-posttest change as improved or deteriorated using the confidence

interval. If the posttest score lies outside of this confidence interval, it is considered to be significantly different from the pretest score. The pre-posttest change is adjusted for regression to the mean. In this study, a 90% confidence interval is used for the independent frailty markers. The scores were dichotomized into decline as (1) vs. no decline (0). For decline in peak expiratory flow, more than 0.5 standard deviation of the difference was used, because reliability analysis of the peak flow measurement is not possible as it is not a scale, and thus the Edwards-Nunnally index cannot be calculated. The cutoffs for perception and new-onset incontinence were based on literature. For change in weight, weight loss in kilograms was used instead decline in BMI, because weight loss was the best criterion in a study to select frail elderly (25). Furthermore, a cutoff point for decline in BMI was not found in the literature. All independent variables were dichotomized so they can be counted and have a straightforward clinical interpretation.

Frailty

Frailty was defined as present when a subject had scores above the cutoff on three or more frailty markers, which is in accordance with Fried et al. (8). The static definition was based on the frailty markers at T_2. The dynamic definition was based on the change in the frailty markers between T_1 and T_2.

Disability

Disability was measured with a questionnaire on self-reported functional limitations at the first follow-up (1995/1996). The respondents were asked the degree of difficulty they had with the following six activities of daily living (ADL): climbing stairs, walking 5 minutes outdoors without resting, getting up from and sitting down in a chair, dressing and undressing oneself, using own or public transportation, and cutting one's own toenails (35). Response categories ranged from (1)" Yes without difficulty" to (5)"No I cannot". The total score was calculated by summing the scores of all activities and ranged between 6 and 30.

Chronic diseases

Seven chronic diseases were examined: chronic obstructive pulmonary diseases, cardiac disease, peripheral arterial disease, diabetes mellitus, cerebrovascular

accidents, rheumatoid arthritis or osteoarthritis and cancer (36). The total number of self-reported chronic diseases at first follow-up (1995/1996) was used for analysis.

Covariates

The analyses were adjusted for age and education. Education was measured with a questionnaire at baseline. The scores ranged from elementary school (low), lower/intermediate general and vocational education (middle), to college and university (high).

Statistical analysis

The association between frailty and mortality was examined in several ways. Separate analyses were performed for men and women, because there were significant interactions between several frailty markers and sex and dynamic frailty and sex. Descriptive t-tests and Chi-square tests were performed to assess differences between those who survived and those who died. For all single static frailty markers, the association with mortality was examined using Cox proportional hazards models adjusted for age and education. For all single dynamic frailty markers, the association was also adjusted for baseline values.

Kaplan-Meier survival curves were used to examine whether the survival of the frail was significantly different of the non-frail. Subsequently, three analyses were performed. First, to examine if frailty predicts mortality, Cox regression analysis was performed for the static and dynamic definition of frailty (three or more frailty markers present). The analyses were adjusted for age and education. Subsequently, to study if the effect of frailty on mortality was independent of chronic diseases and disability, the analyses were adjusted for disability and number of chronic diseases. Additionally, the analyses were adjusted for the other definition of frailty (dynamic when investigating static frailty, and vice versa).

Finally, the association between the number of frailty markers, using both definitions, and mortality was examined using Cox regression analysis. Dummies were used for each count of frailty markers to study the effect of the different numbers of frailty markers with the reference group, the group with no frailty markers. Respondents with five or more markers were pooled together because of small numbers.

Results

Characteristics of the study sample

Table 1 presents the characteristics of the study sample stratified by sex. The mean age at T_2 was 72.5 years for both men and women. Women had more functional limitations and were more likely to have low peak expiratory flow, but men were more likely to decline in peak expiratory flow. Women were more likely to have poor vision, to be incontinent and to have low mastery, more depression, and more often increases in depressive symptoms. Men were less active and more likely to have decreases in hearing capacity from T_1 to T_2 (Table 1). The prevalence of static frailty was higher in women than in men (18% vs. 14%, $P< 0.01$). The prevalence of dynamic frailty was similar in men and women (17% vs. 18%). Seventy-three men (6.9%) were frail in both the static and the dynamic sense. One hundred twenty women (10.0%) were frail in both the static and the dynamic sense. The mean follow-up time until January 1, 2000 was 1291 days after the first follow-up. Between the first follow-up (T_2) and January 1,2000, 328 respondents died: 209 (63.7%) men and 119 (36.3%) women. The respondents who died were significantly older, had fewer years of education, were more frequently unmarried and were more disabled at T_2.

Frailty and mortality

The association with mortality was examined for all single frailty markers (Table 2). Concerning the static frailty markers, low BMI, peak expiratory flow, cognition, depression and physical activity were associated with mortality in both men and women, whereas poor vision was associated with mortality only in women. Concerning the dynamic frailty markers, loss of weight, decline in peak flow, decline in cognition, loss of vision, increase in depressive symptoms, and decline in physical activity were associated with mortality in women. In men, loss of weight and increase in depressive symptoms were associated with mortality.

The mortality in men with static frailty was 50% versus 15% in non-frail men. In static frail women, 27% died compared with 6% in non-frail women. The mortality in men with dynamic frailty was 34% while it was 17% for non-frail men. In women with dynamic frailty, 25% died compared with 7% of non-frail women.

Table 1. Characteristics of the study sample.

Characteristics	Male N=1062 N (%)	Female N=1195 N (%)	P-value	Survived N=1929 N (%)	Died N=328 N (%)	P-value
Mean age at T_2	72.6 (SD8.6)	72.4 (SD8.5)	.603	71.3 (SD8.2)	79.0 (SD7.3)	.000
Death at 1 January 2000	209 (19.7)	119 (10.0)	.000			
Education						
Low	306 (28.8%)	608 (50.9%)	.000	761 (39.5%)	153 (46.6%)	.000
Middle	541 (50.9%)	458 (38.3%)		886 (45.9%)	113 (34.5%)	
High	215 (20.2%)	129 (10.8%)		282 (14.6%)	62 (18.9%)	
Marital status						
Not married	281 (26.4%)	663 (55.3%)	.000	765 (39.7%)	176 (53.7%)	.000
Married	782 (73.6%)	535 (44.7%)		1164 (60.3)	152 (46.3%)	
Mean Functional limitation score T_2 (6-30)	8.4 (SD4.3)	9.9 (SD5.4)	.000	8.6 (SD4.3)	12.7 (SD6.7)	.000
Mean Number of chronic diseases at T_2 (0-7)	1.1 (SD1.1)	1.2 (SD1.1)	.101	1.1 (SD1.0)	1.7 (SD1.3)	.000
Static frailty markers						
BMI<23 at T_2	114 (16.1%)	120 (16.1%)	1.000	174 (14.4%)	60 (24.7%)	.000
Peak flow<250L/Min at T_2	91 (12.8%)	178 (24.2%)	.000	192 (15.9%)	77 (31.3%)	.000
Cognition MMSE<24 at T_2**	127 (12.0%)	140 (11.8%)	.896	169 (8.8%)	98 (30.0%)	.000
Poor vision at T_2	33 (3.1%)	84 (7.0%)	.000	87 (4.5%)	30 (9.2%)	.001
Poor hearing at T_2	126 (12.0%)	115 (9.8%)	.088	174 (9.1%)	67 (21.3%)	.000
Incontinent at T_2	148 (13.9%)	369 (30.9%)	.000	423 (21.9%)	94 (28.7%)	.009
Mastery<14 at T_2	168 (16.5%)	263 (23.2%)	.000	352 (18.9%)	79 (27.1%)	.002
Depression CES-D>16 at T_2	98 (9.5%)	229 (19.9%)	.000	260 (13.8%)	67 (22.5%)	.000
Physical activity<65 min/day at T_2	301 (29.5%)	125 (10.9%)	.000	288 (15.4%)	138 (46.9%)	.000
Dynamic frailty markers						
Weight loss >4 kg T_1-T_2	107 (16.1%)	129 (18.9%)	.197	168 (14.9%)	68 (31.1%)	.000
Decline peak flow >36L/Min T_1-T_2	274 (41.0%)	211 (31.5%)	.000	378 (33.8%)	107 (48.9%)	.000
Decline EN-index* T_1-T_2	179 (17.0%)	187 (15.8%)	.457	259 (13.5%)	107 (32.9%)	.000
Loss of vision T_1-T_2	96 (9.4%)	149 (12.9%)	.010	195 (10.4%)	50 (16.5%)	.003
Loss of hearing T_1-T_2	227 (22.4%)	196 (17.2%)	.003	335 (18.0%)	88 (29.9%)	.000
New incontinence T_1-T_2	82 (7.8%)	133 (11.2%)	.006	175 (9.1%)	40 (12.3%)	.082
Decline Mastery EN-index* T_1-T_2	138 (13.9%)	195 (17.6%)	.020	276 (15.1%)	57 (20.5%)	.027
Decline CES-D EN-index* T_1-T_2	95 (9.3%)	201 (17.5%)	.000	224 (12.0%)	72 (24.6%)	.000
Decline physical activity EN-index* T_1-T_2	220 (22.3%)	266 (24.1%)	.351	418 (23.1%)	68 (24.1%)	.705
Mean number of frailty markers at T_2	1.1 (SD1.2)	1.4 (SD1.4)	.000	1.1 (SD1.2)	2.2 (SD1.6)	.000
Mean number of frailty markers T_1-T_2	1.3 (SD1.2)	1.4 (SD1.2)	.250	1.3 (SD1.2)	2.0 (SD1.5)	.000
Static frail	144 (13.6%)	212 (17.8%)	.007	227 (11.8%)	129 (39.3%)	.000
Dynamic frail	181 (17.0%)	219 (18.3%)	.426	284 (14.7%)	116 (35.4%)	.000
Both static and dynamic frail	73 (6.9%)	120 (10.0%)	.007	117 (6.1%)	76 (23.2%)	.000

* EN-index is the Edwards-Nunnally index.
** MMSE is the Mini Mental State Examination.

Table 2. Associations between single frailty markers and mortality

Frailty markers	Men RR (95%CI)†	Women RR (95%CI)†
Static Frailty markers T_2		
BMI<23	1.5*(1.0-2.2)	1.8*(1.1-2.9)
Low peak flow	2.0***(1.4-2.9)	1.8*(1.1-2.8)
MMSE<24§	1.8**(1.3-2.5)	2.4***(1.6-3.7)
Poor vision	1.4 (0.8-2.7)	1.7*(1.0-2.7)
Poor hearing	1.3 (0.9-1.9)	1.5 (0.9-2.4)
Incontinence	1.1 (0.8-1.6)	1.2 (0.8-1.8)
Low mastery	1.3 (0.9-1.8)	1.2 (0.8-1.8)
Depression	1.6*(1.1-2.3)	1.7**(1.1-2.6)
Low physical activity	2.2***(1.6-2.9)	3.7***(2.4-5.6)
Dynamic Frailty markers T_1-T_2‡		
Weight loss	2.0**(1.3-2.9)	1.8**(1.1-3.0)
Decline peak flow	1.4 (1.0-1.9)	2.6***(1.6-4.1)
Decline cognition	1.2 (0.8-1.6)	2.1***(1.4-3.2)
Loss of vision	0.9 (0.6-1.4)	2.0**(1.3-3.1)
Loss of hearing	1.1 (0.8-1.5)	1.2 (0.8-1.9)
New incontinence	1.1 (0.7-1.7)	1.3 (0.8-2.2)
Decline in mastery	1.1 (0.7-1.6)	1.4 (0.9-2.3)
Increase depressive symptoms	2.4***(1.7-3.5)	2.0***(1.3-3.0)
Decline in physical activity	1.3 (0.8-2.0)	2.1** *(1.3-3.6)

Covariates included age and education.
*P<. 05, **P<. 01, ***P<. 001
† RR (95%CI) Relative Risk and the 95 percent confidence interval
‡ All frailty markers with change between T_1 and T_2 are corrected for the baseline measurement.
§ MMSE Mini Mental State Examination

The survival curves for frail respondents and non-frail respondents were different for both the static and dynamic definition of frailty (P<. 01) (Figure 1a and 1b). For both static and dynamic frailty, those who were frail had a lower probability of surviving than the non-frail.

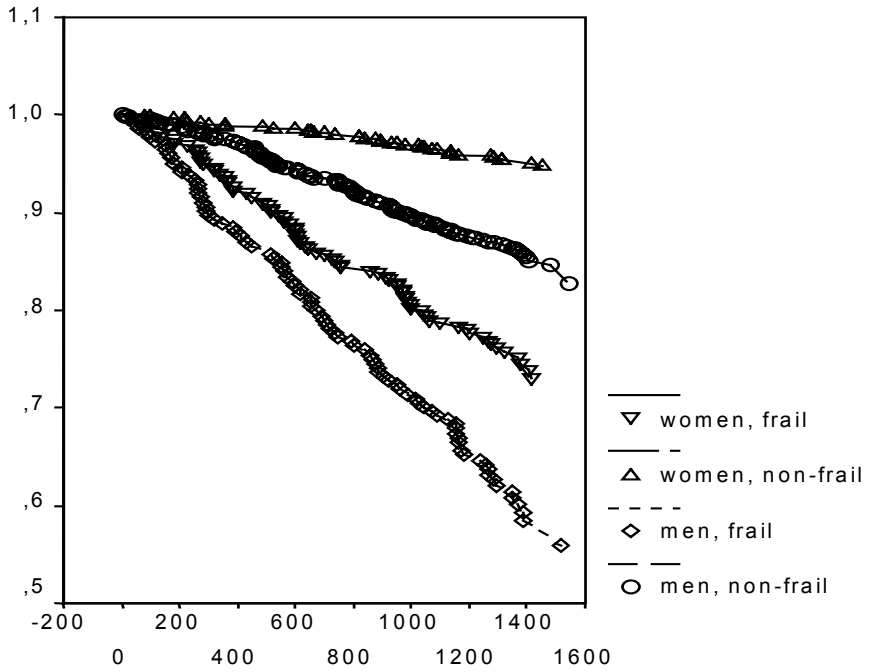

Figure 1a Survival according to frailty status at T_2.

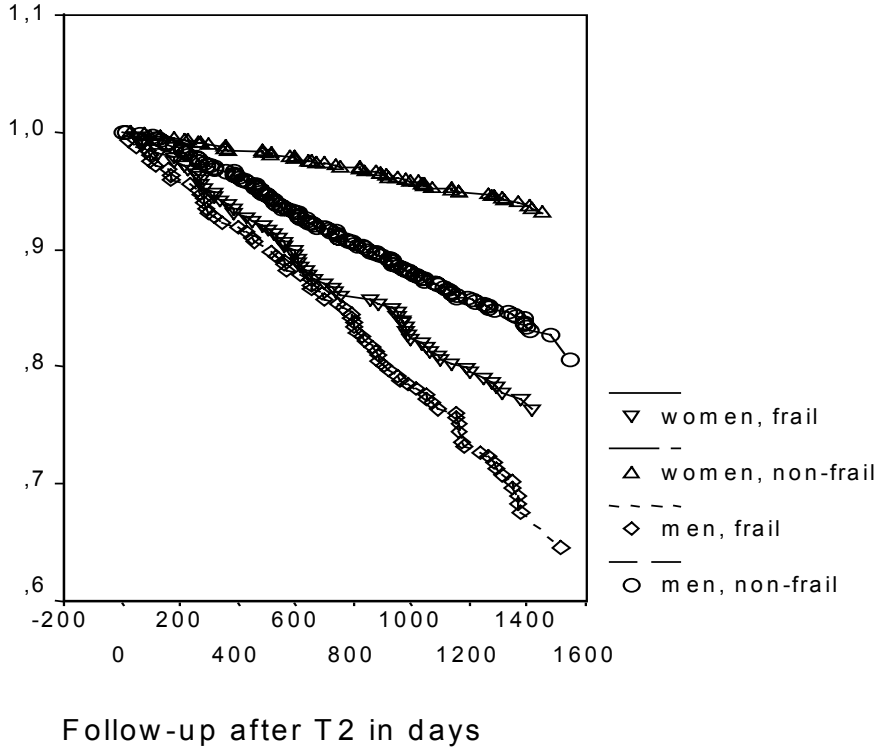

Figure 1b Survival according to frailty status T_1-T_2

The relative mortality risk (RR) for static frailty adjusted for age and education was 2.3 for men (P< .001, 95 percent Confidence Interval (95%CI) 1.7-3.2), and 2.6 for women (P< .001, 95%CI 1.8-3.8) (Figure 2). The relative risk of dynamic frailty was 1.3 for men (P=. 06, 95%CI 1.0-1.8) and 2.5 for women (P< .001, 95%CI 1.8-3.7) (Figure 2).

Disability and chronic diseases

Disability was associated with mortality, with a relative risk of 1.08 for men (P<. 001, 95%CI 1.06-1.11) and 1.09 for women (P<. 001, 95%CI 1.06-1.12) for each point increase (range 6-30). The RR for static frailty adjusted for disability changed to 1.7 for men (P<. 01, 95%CI 1.3-2.4) and 2.1 for women (P<. 01, 95%CI 1.3-3.0) (Figure 2). When adjusting also for the number of chronic diseases the RR's changed to 1.6 for men (P<. 01, 95%CI 1.2-2.3) and 2.0 for women (P<. 01, 95%CI 1.4-3.0) (Figure 2).

The RR for dynamic frailty adjusted for disability changed to 1.3 for men (P>. 05, 95%CI 0.9-1.7) and 2.1 for women (P<. 001, 95%CI 1.5-3.1) (Figure 2). When the relative mortality risk for frailty was also adjusted for the number of chronic diseases the RR changed to 1.2 for men (P>. 05, 95%CI 0.9-1.6) while the RR for women remained unchanged (P<. 001, 95%CI 1.4-3.1) (Figure 2). When the analyses of static frailty were additionally adjusted for the presence of dynamic frailty, the RR for men changed in 1.6 (P<. 01, 95%CI 1.2-2.3), and for women in 1.6 (P<. 05, 95%CI 1.1-2.5). When the analyses for dynamic frailty were additionally adjusted for the presence of static frailty, the RR for men changed in 1.0 (P> .05, 95%CI 0.7-1.4), and for women in 1.8 (P<. 01, 95%CI 1.2-2.7).

Number of frailty markers and mortality

Cox regression analysis was performed using dummies for each count of frailty markers to study the effect of different numbers of frailty markers based on the static and dynamic definitions of frailty. The mortality risk increased with an increase in the total number of static frailty markers in both men and women (Table 3). However, the mortality risk increased with an increase in the total number of dynamic frailty markers only in women, but not in men (Table 3).

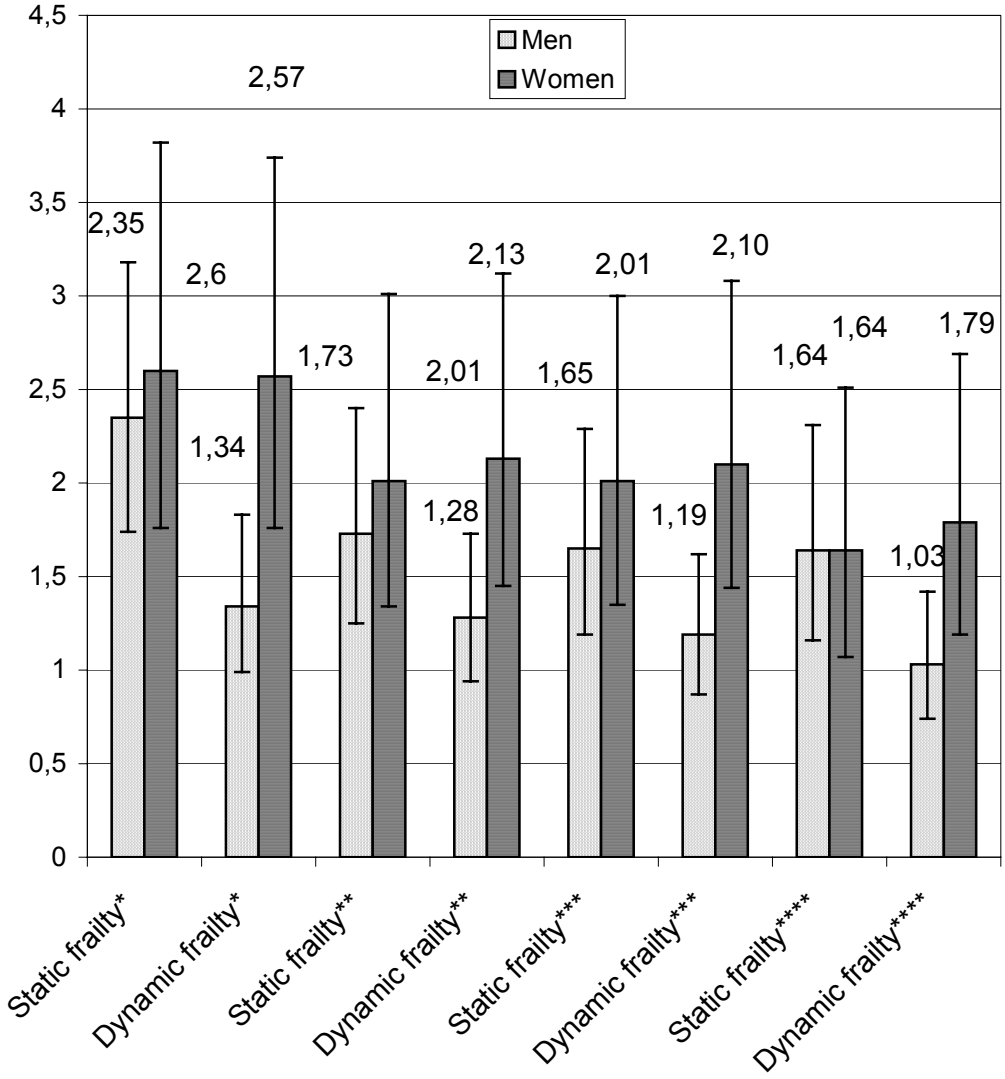

Figure 2. Relative risks for men and women

Static frailty = the presence of three or more frailty markers at T_2
Dynamic frailty = change between T_1 and T_2 in three or more frailty markers.
* Adjusted for age and education; ** adjusted for age, education and disability; *** adjusted for age, education disability and total number of chronic diseases (7 possible chronic diseases: chronic obstructive pulmonary diseases, cardiac disease, peripheral arterial disease, diabetes mellitus, cerebrovascular accidents, rheumatoid arthritis or osteoarthritis and cancer). Disability is measured with a self-reported questionnaire ranging from 6 (all activities without difficulty) to 30 (not able to do for all activities).
**** Adjusted for age, education, disability, total number of chronic diseases and the other frailty (dynamic when examining the effect of static frailty and static frailty when examining the effect of dynamic frailty

Table 3. Associations between number of frailty markers and mortality

Frailty markers	RR (95%CI) # Men N=1062	RR (95%CI) # Men N=1062	RR (95%CI) # Women N=1195	RR (95%CI) # Women N=1195
Static frailty markers				
0 (reference group)	1	1	1	1
1	1.57* (1.04-2.38)	1.46 (0.96-2.22)	0.92 (0.44-1.94)	0.80 (0.38-1.70)
2	1.68* (1.07-2.64)	1.31 (0.82-2.08)	2.49** (1.27-4.88)	1.76 (0.88-3.56)
3	3.72*** (2.34-5.90)	2.41*** (1.48-3.95)	3.33*** (1.63-6.81)	2.46* (1.18-5.12)
4	2.70*** (1.54-4.72)	1.80* (1.01-3.21)	4.47*** (2.10-9.55)	2.91** (1.32-6.44)
5 and more	3.62*** (1.75-7.48)	1.84 (0.85-3.97)	4.94*** (2.17-11.3)	2.41 (0.99-5.89)
Education (high=ref))	1	1	1	1
Education (low)	0.97 (0.68-1.39)	1.00 (0.70-1.44)	0.86 (0.49-1.50)	0.74 (0.42-1.30)
Education (middle)	0.69* (0.48-0.99)	0.66 (0.46-0.95)	0.92 (0.49-1.69)	0.82 (0.45-1.53)
Age at T_2	1.08*** (1.06-1.10)	1.07*** (1.05-1.09)	1.09*** (1.06-1.12)	1.07*** (1.04-1.11)
Disability (6-30)†		1.06*** (1.03-1.09)		1.05** (1.02-1.09)
No. chronic diseases (range 0-7)‖		1.23** (1.09-1.38)		1.23** (1.05-1.44)
Dynamic Frailty markers				
0 (reference group)	1	1	1	1
1	0.85 (0.57-1.27)	0.85 (0.57-1.28)	0.84 (0.42-1.69)	0.79 (0.39-1.58)
2	1.01 (0.66-1.54)	0.98 (0.64-1.50)	1.76 (0.94-3.28)	1.54 (0.83-2.89)
3	1.16 (0.73-1.82)	1.04 (0.66-1.65)	2.42** (1.25-4.65)	1.90 (0.98-3.69)
4	1.35 (0.73-2.49)	1.09 (0.59-2.01)	4.61*** (2.30-9.25)	3.14** (1.54-6.38)
5 and more	1.81 (0.83-3.92)	1.59 (0.73-3.43)	4.57** (1.82-11.44)	3.84** (1.52-9.67)
Education (high=ref)	1	1	1	1
Education (low)	0.98 (0.69-1.42)	0.98 (0.68-1.40)	0.79 (0.45-1.39)	0.69 (0.39-1.22)
Education (middle)	0.66* (0.46-0.96)	0.63* (0.44-0.90)	0.78 (0.42-1.44)	0.75 (0.40-1.38)
Age at T_2	1.10*** (1.08-1.12)	1.08*** (1.05-1.10)	1.10*** (1.07-1.13)	1.08*** (1.05-1.11)
Disability (6-30)†		1.07*** (1.04-1.10)		1.06** (1.02-1.09)
No. chronic diseases (range 0-7)‖		1.24*** (1.11-1.40)		1.23** (1.06-1.43)

*P<. 05, **P<. 01, ***P<. 001

RR (95CI) Relative Risk and 95 percent confidence interval. The first column for men and women are adjusted for age and education. The second column for men and women are adjusted for age, education, disability and number of chronic diseases. The high-educated group is the reference group.

†Disability ranges between 6-30 with 6 all activities without difficulty and 30 all activities impaired, the RR is per point increase.

‖ 7 possible chronic diseases: chronic obstructive pulmonary diseases, cardiac disease, peripheral arterial disease, diabetes mellitus, cerebrovascular accidents, rheumatoid arthritis or osteoarthritis and cancer.

Discussion

In this prospective population-based study, the effect of frailty on mortality among men and women was investigated. Frailty was defined as present when a subject had scores above the cutoff of three or more frailty markers. Moreover, the effects of a static and dynamic definition of frailty were investigated whereas other studies so far have used a static definition of frailty (3;8;18). Static frailty was associated with

mortality in men and women. Dynamic frailty was associated with mortality in women only.

These results have led to the conclusion that the mortality risk of frailty was independent of the effect of disability and chronic diseases. When disability was included, static frailty still had an effect on mortality in both men and women, but the effect was weakened. The same was true for the effect of dynamic frailty in women. When the number of chronic diseases was included, this did not change the results. Furthermore, static frailty had an effect independent of dynamic frailty in both men and women. Dynamic frailty had an effect independent of static frailty only in women.

In this study, women had more frailty markers than men, and the prevalence of frailty was twice as high in women as in men, but more men died during the follow-up period. Moreover, more single frailty markers were associated with mortality in women than in men. It seems that men in our study more often died suddenly whereas women showed a steady progressive decline. Our findings are supported by the findings of other studies. Fried et al. (8) found that more women than men were frail. Also men have been shown to have higher age-adjusted death rates of all causes, while women have more morbidity (37-39). A study of Mitniski et al. (18), showed that their frailty index was associated with mortality, but their mortality data were not linked on an individual basis. Nevertheless, they observed that women accumulate more deficits than men of the same age but men have a higher risk of mortality. Another study determined four patterns of functional decline and also showed that frail subjects were most likely to be women who were relatively more disabled throughout the last year of life, whereas men died more suddenly and more often of cancer (40). Walston & Fried suggested that frailty is more frequent in women because men have higher baseline levels of muscle mass and higher levels of neuroendocrine and hormonal factors (testosterone) that may protect them from reaching frailty (6). The sex-differences in the relationship between frailty and mortality should be further investigated.

Our finding of an increasing risk of mortality when the number of frailty markers increases is in agreement with Rockwood et al. (3). In that study, subjects were classified at four levels from fitness to frailty and the relative risks ranged from 1.2 for people living in the community to 3.3 for the most frail. Mitniski et al. (17) concluded that the number of deficits might be the most important determinant of mortality rather than the precise nature.

In the study by Fried et al., five frailty markers were investigated with emphasis on the physiologic markers. In this study, nine frailty markers were included which automatically increases the risk for each individual to have three or more markers. Therefore, the prevalence of frailty was higher in this study. Nevertheless, the relative risks for mortality in this study are comparable with the study by Fried et al (8).

Our study supports evidence from previous studies in several ways. First, we found a risk of death for frailty similar to that found by Fried et al (8). Second, it confirms the importance of inactivity, weight loss, cognitive functioning and vision as frailty markers (3;8;11;25). Our study also contributes to the literature not only in that it distinguishes between sexes but also in that it introduces measures of dynamic frailty and that it includes psychological frailty markers. The dynamic definition of frailty is an important contribution to the measurement of frailty. It is possible that a person is frail in a dynamic but not in a static sense, meaning that this person declines from a high level of functioning to a lower level of functioning but not to a very low level of functioning (static frailty). A person who declines from a high level of functioning to a lower level of functioning but not the lowest is defined as frail only if he or she declines in three or more areas, which represents multisytem decline. This person might experience a loss in reserve capacity threatening the homeostatic balance.

In this study, psychological frailty markers such as depression, cognitive function and mastery were included, whereas other studies used physiological measures only. Recent reviews suggested that so far frailty has been studied with a biomedical perspective and psychological aspects should be taken into account (20;21). In this study, the psychological frailty markers cognition and depression contributed to the prediction of mortality in both men and women, but mastery did not. An important part of the definition of frailty is the high risk of adverse outcomes due to a precarious balance. Psychological resources will influence how people cope with their physical problems.

A limitation of this study is the exclusion of all people lost to follow-up or because of missing values on the disability questionnaire. These respondents are more likely to be frailer than the included respondents. Another limitation of our study is that all independent variables were dichotomized; suggesting that information about the subjects may have been lost. However, dichotomized frailty markers are

easily applicable in medical practice. A third limitation may be the lack of adjustment for smoking. We examined smoking (current, former and never smoked) in preliminary analyses and found it not to be a confounder in the relationship between frailty and mortality; therefore, the analyses were not adjusted for smoking. An additional limitation is that six of the nine frailty markers were based on self-report. However the reliability of the physical activity questionnaire has been investigated and was reasonably good (33). For the other markers we found that most were more frequent in women than in men. It is possible that women answered differently from men, but in a representative population-based study it is not often possible to include performance based test for all measurements, because costs, time and complexity preclude their administration in the home. A final limitation is the time interval of three years between two measurement cycles of LASA, which is a relatively long period. It is possible that change over three years is too long to define frailty. It is possible that frailty develops more quickly and that the frailest people died before the second measurement. This may be especially true for young-old men. In a study design with more frequent measurement cycles, dynamic frailty may be more predictive of mortality in men.

The importance of developing an instrument for finding moderately frail people was shown in a recent study. An intervention study among physically frail elderly persons living at home showed that persons who were moderately frail benefited the most from the intervention, whereas those with severe frailty had worsening disability over time, despite the intervention (41). More research is needed to study the psychological frailty markers in combination with physical frailty markers. Eventually a frailty instrument may be developed to screen the older population. In the frail people thus detected, interventions might be applied to postpone adverse outcomes.

In conclusion, static frailty was a strong predictor for mortality for both men and women. The association with mortality was stronger for women than for men. In women, frailty was associated with mortality even when adjusting for disability and chronic diseases.

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Chapter 5

Endocrine and inflammatory markers as predictors of frailty

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Abstract

Objective: To examine the association of serum concentrations of 25-hydroxyvitamin D (25(OH)D), interleukin-6 (IL-6), C-reactive protein (CRP), and insulin-like growth factor-1 (IGF-1) with prevalent and incident frailty.

Methods: The sample was derived from The Longitudinal Aging Study Amsterdam, a prospective general population-based cohort study with three-yearly measurement cycles. The respondents were men and women aged 65 and over, who participated at T_1 (1995/1996, N=1720) and T_2 (1998/1999, N=1509). Blood samples were obtained at T_1 (N=1271). The presence of frailty at T_1 and 3-year incidence of frailty. Frailty is defined as the presence of three out of nine frailty indicators.

Results: At T_1, 242 (19.0%) of all respondents were frail. Those who were frail at T_1 had higher CRP and lower 25(OH)D levels. Serum 25(OH)D remained associated with frailty after adjustment for potential confounders with odds ratios of 2.60 (95%CI 1.60-4.21) for 25(OH)D< 25nmol/l and 1.72 (95%CI 1.19-2.47) for 25(OH)D 25-50 nmol/l versus high levels of 25 (OH)D. Of the non-frail at T_1, 125 respondents (14.1%) became frail at T_2. After adjustment, moderately elevated CRP levels (3-10 ug/ml) (OR 1.69, 95%CI 1.09-2.63) and low 25(OH)D (OR 2.04, 95%CI 1.01-4.13) were associated with incident frailty. No consistent associations were observed for IL-6 and IGF-1.

Conclusion: Low 25(OH)D levels were strongly associated with prevalent and incident frailty; moderately elevated levels of CRP were associated with incident frailty.

Introduction

Frailty is a term used to describe an older person at risk for adverse outcomes such as physical decline (1), disability (1;2), nursing home admission (2) and mortality (1;3;4). Frailty consists of multisystem decline (1;5) and is considered to be a consequence of changes in neuromuscular, endocrine and immune functioning which occur as people age (5;6). Fried et al. hypothesized a negative spiral in which inflammation, neuroendocrine deregulation and sarcopenia results in frailty (7). However, there is little empirical evidence for the role of endocrine and inflammatory markers of frailty.

There are several reasons to expect that inflammatory and endocrine markers are associated with frailty. First, studies have shown that the levels of inflammatory markers, such as IL-6 and CRP increase with aging, and that elevated levels are associated with disability and mortality (8-11). High levels of cytokines may induce skeletal muscle loss and aggravate neuroendocrine deregulation (7;12). Furthermore, vitamin D deficiency is common in older persons, with a gradual decline in levels from healthy to dependent and institutionalized individuals (13). Low serum 25-hydroxyvitamin D (25(OH)D) is associated with muscle weakness (14), sarcopenia (15), falls (16) and disability (13). Growth hormone and insulin-like growth factor-1 (IGF-1) decrease with age (17) and may play a role in the maintenance of muscle mass and functioning with aging (18). Interaction between IGF-1 and IL-6 in relation to disability has also been reported (8).

Only a few investigators have studied the direct relation between biological markers and frailty (19-21). Most studies investigating endocrine and inflammatory markers so far have focused on outcomes such as disability, mobility and mortality (8-11;22). Furthermore, the relation between frailty, endocrine markers and inflammation has been investigated in cross-sectional studies only, which makes it difficult to draw conclusions on the predictive value of the endocrine and inflammatory markers for frailty. The aim of this study was to examine the associations between endocrine and inflammatory markers and frailty, cross-sectionally and prospectively in the subsequent three years in a population-based study of men and women aged 65 and over.

Methods

Study population

The data were collected in the context of the Longitudinal Aging Study Amsterdam (LASA). LASA is an ongoing multidisciplinary study on predictors and consequences of changes in physical, cognitive, emotional and social functioning in older people in the Netherlands. A random sample stratified by age and gender according to expected mortality after 5 years, was drawn from population registers of eleven municipalities in three geographical areas in the Netherlands. At each cycle, data were collected in a face-to-face main interview, carried out in the subjects' home or institutional residence, by specially trained interviewers, followed by a medical interview two to six weeks later. The details of the LASA study have been described elsewhere (23) (see also http://ssg.scw.vu.nl/lasa/). The Medical Ethics Committee of the VU University Medical Center approved the study and informed consent was obtained from all respondents.

The sample for this study consisted of respondents who participated in the main interview at the first follow-up measurement T_1 (1995/996) and were asked to participate in a medical interview (inclusion criterion for a medical interview 1995/1996 age 65 years and older, N=1720). Of the 1720 respondents that were eligible for the medical interview, 1509 participated (87.7%). Blood samples were obtained from 1321 respondents. In 1285 of these respondents, all four serum markers were determined (74.7%). For the cross-sectional analyses, 14 respondents were excluded because of missing covariates leaving a sample of 1271 respondents. The non-responders at baseline (1995/1996) were older, had more cognitive problems and chronic diseases, and a lower education level. There were no sex differences in non-response.

For the prospective analyses with 3-years follow-up, 231 of the 1271 respondents were lost to follow-up; 159 respondents died, 12 respondents refused, 11 were not able to participate due to physical or cognitive problems, 6 respondents could not be contacted and 43 respondents were excluded because no information on the frailty indicators was available. Of the remaining 1040 respondents for the prospective analyses, the respondents who were frail at baseline were excluded to study the effect of serum endocrine and inflammatory markers on incident frailty,

leaving a sample of 885 respondents. Those lost to follow-up had more often higher levels of IL-6 and CRP, and had more often lower levels of IGF-1 and 25(OH)D. Those lost to follow-up were older, had more cognitive problems, and had more depressive symptoms, more chronic diseases and more frailty markers present at baseline.

Measures

Serum endocrine and inflammatory markers

Morning blood samples were obtained in 1995/1996. The participants were allowed only tea and toast. The samples were centrifuged and serum was stored at -70°C until measurement.

Serum 25-hydroxyvitamin D (25(OH)D) was measured according to a competitive protein-binding assay (Nichols Diagnostics, San Capistrano, CA, USA). Insulin-like growth factor 1 (IGF-1) was determined by immunoradiometric assay after extraction (DSL, Webster, TX, USA). These analyses were carried out at the Endocrine Laboratory of the VU University Medical Center, Amsterdam.

The serum concentrations of C-Reactive Protein (CRP) and interleukin-6 (IL-6) were determined using sensitive regular immunoassays (ELISA) at Sanquin Research, Amsterdam. The IL-6 ELISA was obtained from the Business Unit Immune Reagents of Sanquin, and performed according to manufacturer's instructions. CRP levels were measured with a sandwich-type ELISA in which polyclonal rabbit anti-CRP antibodies were used as catching antibodies and a biotinylated mAb against CRP (CLB anti-CRP-2) as the detecting antibody. CRP and IL-6 were measured in duplicate, with averages being reported.

The detection limit was 10 nmol/l for 25(OH)D, 1 nmol/l for IGF-1, 0.8 ng/mL for CRP, and 5.0 pg/ml for IL-6. Recombinant IL-6, purified CRP and pooled human plasma were used as standards in the respective assays. The inter-assay coefficient of variation (CV) was < 4.2% for CRP, < 5% for IL-6, < 14% for IGF-1, and < 15 % for 25(OH)D.

Frailty

Nine frailty indicators were used to determine frailty. Both physical and psychological frailty indicators were included (see (4) for an extensive description). The nine frailty indicators included low body mass index (BMI<23 kg/m^2), low peak expiratory flow

(lowest quintile ≤ 270 l/min (24)), cognitive functioning (MMSE<24 (25)), poor distant vision and hearing problems (able to see or hear with much difficulty or not able (26)), incontinence (27), low sense of mastery (short version of the Pearlin & Schooler mastery scale, lowest quintile ≤14 (28)), depressive symptoms (CES-D score ≥ 16 (29)) and physical activity (LASA Physical Activity Questionnaire, lowest quintile<66 min/day (30)).
The definition of frailty in this study was the presence of three or more out of nine frailty indicators. Also the number of frailty indicators was used as an outcome.

Covariates
The analyses were adjusted for age, sex, education, season of blood sampling, use of prescribed anti-inflammatory drugs [nonsteroidal anti-inflammatory drugs (NSAID's), aspirin and corticosteroids], use of estrogens, smoking status, alcohol consumption, obesity, high intensity physical activity, levels of parathyroid hormone (PTH) and chronic disease.

The presence of chronic diseases, the use of estrogens, smoking, obesity and alcohol consumption increase the levels of inflammatory markers and are associated with frailty (31-34). High intensity physical activity decreases the production of inflammatory markers and is inversely associated with frailty (31;34). The season of blood sampling was included (spring/summer versus autumn/winter) because the serum concentrations of 25(OH)D are influenced by sunlight exposure (13). High serum concentrations of parathyroid hormone (PTH) are associated with low 25(OH)D (15). Lower education levels are associated with more chronic disease, a less healthy lifestyle and frailty (32), and were therefore included in all analyses.

The respondents were asked about their highest level of education attained, which was categorized into three categories (low, middle and high). Serum concentration of PTH was measured by immunoradiometric assay (Incstar Corp., Stillwater, MN, USA) and was used as a continuous variable in the analyses. The interviewers inspected medication bottles, and the medication was recorded if it was prescribed by a general practitioner and used in the two weeks before the interview. Smoking status was divided into never smoker vs. other and alcohol consumption was divided into never drinker vs. other. Alcohol use was also examined with more categories (moderate and excessive drinking), but preliminary analyses showed that these groups did not differ in their associations with frailty and they were therefore

grouped together. Obesity was defined as a Body Mass Index (BMI) ≥30 kg/m^2. High intensity physical activity (yes/no) was based on the following activities with a MET (Metabolic Equivalent) score ≥ 5.0: distance walking, cycling, swimming, dancing, jogging, rowing, playing tennis, soccer, basketball, volleyball and winter sports. Metabolic Equivalents (MET scores) are used to express the intensity of a specific activity; it is the ratio of work metabolic rate for a specific activity divided by the resting metabolic rate. Seven self-reported chronic diseases were examined: chronic obstructive pulmonary diseases, cardiac disease (myocardial infarction, arrhythmias, congestive heart failure, angina pectoris and narrowing of the coronary arteries), peripheral arterial disease, diabetes mellitus, cerebrovascular accidents, rheumatoid arthritis or osteoarthritis (both conditions were grouped together because respondents appeared to find it hard to differentiate between them) and cancer. These chronic diseases are the most frequent in the Dutch older population with a prevalence of at least five percent. Agreement between respondents' self-reported data and data from the general practitioner has been shown to be satisfactory or good for most diseases studied (35). Respondents could answer yes or no.

Statistical analyses

Serum 25-hydroxyvitamin D was categorized into three groups: <25, 25-50, >50 nmol/l (13). The highest group was the reference group. Insulin-like growth factor was dichotomized at the lowest ten percent (below 7.7 nmol/l) as these levels were shown to be associated with low walking speed (36). IL-6 was dichotomized at the detection limit (5 pg/ml) with low as reference group. Because of the large numbers of respondents below the detection limit, it was not possible to divide IL-6 into more categories. CRP was categorized into: <3, 3-10, >10 µg/ml. Values >3 µg/ml are frequently used to indicate an increased risk of adverse outcomes (37), while values >10 µg/ml indicate clinically relevant inflammation (38). The low group (<3µg/ml) was used as the reference group.

Both T-tests and Chi-square tests were performed to assess differences between those who were frail and those who were not frail at baseline. For the examination of the cross-sectional association, logistic regression analyses were performed for each of the endocrine and inflammatory markers with the presence of frailty as outcome measure. The first model included only the single serum markers, sex and age. In the second model, season of blood sampling (only for 25(OH)D), use

of anti-inflammatory drugs (only for CRP and IL-6), smoking status, alcohol use, estrogen use, obesity (only for CRP and IL-6), and physical activity (only for CRP and IL-6) were included. For all serum markers, the interaction with sex, and the interactions between the serum markers were studied ($p<0.10$). In the final model, chronic disease and PTH (PTH only for 25(OH)D) were added, to study if PTH and chronic diseases mediated the relation between the endocrine and inflammatory markers and frailty. All serum markers were finally included in a single model to study their associations with frailty adjusted for each other.

For the examination of the prospective association, logistic regression analyses were performed to study whether serum markers predicted incident frailty. The consecutive logistic regression models were similar to those of the cross-sectional analyses.

As an additional outcome variable, the total number of frailty indicators was used and associations were tested with multinomial logistic regression analysis. The group without any frailty indicators was the reference group. For the cross-sectional analysis, respondents with four or more frailty indicators were grouped because of small numbers. In the prospective analysis, respondents with three or more frailty indicators were grouped together because of small numbers. Analyses were adjusted for baseline number of frailty indicators and for the confounders listed above.

Results

Characteristics of the sample

There were 242 (19.0%) frail respondents at baseline (1995/1996). Frail respondents were more often women, older (79.2 vs. 74.5 years), had more chronic diseases, had more often low serum concentration of 25(OH)D and had more often higher serum concentration of CRP (Table 1, left segment). Frail respondents also more often had a lower level of education, higher BMI, higher serum PTH, and smoked and used alcohol less often.

One hundred and twenty-five respondents (14.1%) who were not frail at baseline became frail after three years (T_2, 1998/1999). They were older and had more often lower serum concentrations of 25(OH)D and IGF-1 and had more often higher serum concentrations of CRP at baseline (Table 1, right segment).

Cross-sectional analyses of frailty

Low serum 25(OH)D concentrations were significantly associated with frailty when adjusting for sex and age (model 1, Table 2). Compared to high serum 25(OH)D, the Odds Ratio (OR) for low serum 25(OH)D was 2.95 (95% confidence interval (95%CI) 1.87-4.65), and 1.85 (95%CI 1.31-2.60) for moderately low serum 25(OH)D. The OR's decreased to 2.60 (95%CI 1.60-4.21) and 1.72 (95%CI 1.19-2.47) (model 3) when adjusting for all confounders. There was no significant cross-sectional association of CRP, IGF-1, and IL-6 with frailty when adjusting for all confounders. When the serum markers were adjusted for each other, the results were similar. There was no interaction between the serum markers or between the serum markers and sex cross-sectionally.

Prospective analyses of frailty

Moderately elevated serum concentrations of CRP (3.0-10.0 µg/ml) predicted frailty, with an OR of 1.77 (95%CI 1.15-2.68) versus low serum concentration of CRP when adjusting for sex and age (Table 3). The OR decreased to 1.69 (95%CI 1.09-2.63) when adjusting for all confounders. Low serum 25(OH)D was also significantly associated with incident frailty with an OR of 2.04 (95%CI 1.01-4.13) versus high serum 25(OH)D when adjusting for all confounders. When including all biological markers in a model, the OR of serum CRP did not change but the OR for low serum 25(OH)D changed to 1.90 (95%CI 0.92-3.95). There was no significant prospective association of serum IGF-1 and serum IL-6 with incident frailty when adjusting for all confounders. Again, there was no interaction between the serum markers or between the serum markers and sex.

Table 1. Characteristics of the study sample

Baseline characteristics	Cross-sectional analyses			Prospective analyses		
	Not frail at T_1 N=1,029	Frail at T_1 N=242	P-value	Not frail at T_2 N=760	Frail at T_2 N=125	P-value
Endocrine and inflammatory markers						
25 (OH)D<25nmol/l	85 (8.3%)	56 (23.2%)	.000	46 (6.1%)	20 (16.0%)	.000
25-50 nmol/l	355 (34.5%)	116 (47.9%)		254 (33.4%)	51 (40.8%)	
>50 nmol/l	589 (57.2%)	70 (28.9%)		460 (60.5%)	54 (43.2%)	
IGF-1 ≤7.7 nmol/l	97 (9.4%)	33 (13.6%)	.052	60 (7.9%)	19 (15.2%)	.008
IL-6 ≥ 5.0 pg/ml	111 (10.8%)	28 (11.6%)	.725	69 (9.1%)	15 (12.1%)	.302
CRP < 3.0 ug/ml	525 (51.0%)	95 (39.3%)	.004	424 (55.8%)	53 (42.4%)	.006
3.0-10.0 ug/ml	359 (34.9%)	102 (42.1%)		242 (31.8%)	58 (46.4%)	
>10.0 ug/ml	145 (14.1%)	45 (18.6%)		94 (12.3%)	14 (11.3%)	
Number of frailty indicators present at baseline						
0	362 (35.2%)	0	.000	309 (40.7%)	13 (10.4%)	.000
1	399 (38.8%)	0		303 (39.9%)	43 (34.4%)	
2	268 (26.0%)	0		148 (19.5%)	69 (55.2%)	
3	0	136 (56.2%)		0	0	
4	0	106 (43.8%)				
Covariates						
Women (%)	498 (48.4%)	151 (62.4%)	.000	378 (49.7%)	69 (55.2%)	.258
Mean age (SD)	74.5 (6.3)	79.2 (6.2)	.000	73.4 (5.9)	78.2 (6.2)	.000
Low level of education	399 (38.8%)	132 (54.5%)	.000	277 (36.4%)	57 (45.6%)	.082
Middle level of education	481 (46.7%)	76 (31.4%)		378 (49.7%)	49 (39.2%)	
High level of education	149 (14.5%)	34 (14.0%)		105 (13.8%)	19 (15.2%)	
Mean no. chronic diseases (SD)	1.1 (1.0)	1.6 (1.1)	.000	1.0 (0.9)	1.3 (1.1)	.002
BMI>30 kg/m^2	196 (19.0%)	62 (25.6%)	.022	147 (19.3%)	29 (23.2%)	.317
Mean PTH pmol/l (SD)	3.5 (1.9)	4.2 (2.5)	.000	3.4 (1.8)	3.6 (1.4)	.185
High intensity physical activity (yes/no)	211 (20.5%)	18 (7.4%)	.000	181 (23.8%)	18 (14.4%)	.019
Never smoked	339 (33.0%)	111 (45.9%)	.000	255 (33.6%)	47 (37.6%)	.376
Ever smoked	690 (67.1%)	131 (54.1%)		505 (66.4%)	78 (62.4%)	
No alcohol use	224 (21.8%)	89 (36.8%)	.000	159 (20.9%)	24 (19.2%)	.660
Alcohol use	805 (78.2%)	153 (63.2%)		601 (79.1%)	101 (80.8%)	
Use of anti-inflammatory drugs	277 (26.9%)	88 (36.4%)	.003	183 (24.1%)	43 (34.4%)	.014
Use of estrogens	9 (0.9%)	4 (1.7%)	.279	6 (0.8%)	2 (1.6%)	.375

Table 2. Odds Ratio's (with 95%CI) from cross-sectional logistic regression analyses of the association of four serum markers and prevalent frailty (N=1271)

N	Serum marker	Model 1	Model 2	Model 3	Model 4
1132	IL-6 <5 pg/ml	1	1	1	1
139	IL-6 ≥5 pg/ml	0.98 (0.62-1.57)	0.96 (0.60-1.53)	0.94 (0.58-1.53)	0.75 (0.44-1.27)
620	CRP <3.0 ug/ml	1	1	1	1
461	CRP 3.0-10.0 ug/ml	1.35 (0.99-1.89)	1.27 (0.91-1.78)	1.20 (0.85-1.69)	1.14 (0.80-1.61)
190	CRP >10.0 ug/ml	**1.64 (1.07-2.50)**	1.46 (0.95-2.25)	1.37 (0.88-2.13)	1.37 (0.85-2.19)
141	25(OH)D <25 nmol/l	**2.95 (1.87-4.65)**	**3.04 (1.92-4.82)**	**2.60 (1.60-4.21)**	**2.55 (1.56-4.17)**
471	25(OH)D 25-50 nmol/l	**1.85 (1.31-2.62)**	**1.88 (1.32-2.67)**	**1.72 (1.19-2.47)**	**1.66 (1.15-2.40)**
659	25(OH)D >50 nmol/l	1	1	1	1
130	IGF-1 ≤ 7.7 nmol/l	1.02 (0.65-1.60)	0.98 (0.62-1.54)	1.01 (0.64-1.61)	0.88 (0.54-1.41)
1141	IGF-1 >7.7 nmol/l	1	1	1	1

In bold P < .05
Model 1: single endocrine and inflammatory markers, adjustment for age and sex.
Model 2: single endocrine and inflammatory markers, additional adjustment for IL-6 and CRP, education, use of anti-inflammatory drugs, use of estrogen, obesity, physical activity, smoking status, and alcohol consumption. For 25(OH)D, additional adjustment for education, season of blood sampling, smoking status and alcohol consumption. For IGF-1, additional adjustment for education, smoking status and alcohol consumption.
Model 3: single endocrine and inflammatory markers, additional adjustment for the self-reported chronic diseases: Cardiac disease, peripheral arterial disease, diabetes mellitus, arthritic disease, chronic obstructive pulmonary disease, stroke and cancer. For 25(OH)D, additional adjustment for PTH.
Model 4: All endocrine and inflammatory markers in model, adjustment for all confounders.

Table 3. Odds Ratio's (with 95%CI) from prospective logistic regression analyses of the association of four serum markers and incident frailty (N=885)

N	Serum marker	Model 1	Model 2	Model 3	Model 4
801	IL-6 <5 pg/ml	1	1	1	1
84	IL-6 ≥5 pg/ml	1.08 (0.58-2.02)	1.00 (0.53-1.89)	1.03 (0.54-1.97)	0.93 (0.47-1.84)
477	CRP <3.0 ug/ml	1	1	1	1
300	CRP 3.0-10.0 ug/ml	**1.77 (1.15-2.68)**	**1.72 (1.11-2.65)**	**1.69 (1.09-2.63)**	**1.70 (1.09-2.67)**
108	CRP >10.0 ug/ml	1.27 (0.66-2.45)	1.23 (0.63-2.39)	1.17 (0.69-2.31)	1.13 (0.56-2.27)
66	25(OH)D <25 nmol/l	1.89 (0.98-3.63)	**2.02 (1.03-3.94)**	**2.04 (1.01-4.13)**	1.90 (0.92-3.95)
305	25(OH)D 25-50 nmol/l	1.14 (0.73-1.77)	1.21 (0.77-1.89)	1.30 (0.82-2.07)	1.24 (0.77-2.00)
514	25(OH)D >50 nmol/l	1	1	1	1
79	IGF-1 ≤ 7.7 nmol/l	1.42 (0.79-2.57)	1.53 (0.84-2.80)	1.47 (0.79-2.72)	1.40 (0.74-2.62)
806	IGF-1 >7.7 nmol/l	1	1	1	1

In bold P < .05
Model 1: single endocrine and inflammatory markers, adjustment for age and sex.
Model 2: single endocrine and inflammatory markers, additional adjustment for IL-6 and CRP, education, use of anti-inflammatory drugs, use of estrogen, obesity, physical activity, smoking status, and alcohol consumption. For 25(OH)D, additional adjustment for education, season of blood sampling, smoking status and alcohol consumption. For IGF-1, additional adjustment for education, smoking status and alcohol consumption.
Model 3: single endocrine and inflammatory markers, additional adjustment for the self-reported chronic diseases: Cardiac disease, peripheral arterial disease, diabetes mellitus, arthritic disease, chronic obstructive pulmonary disease, stroke and cancer. For 25(OH)D, additional adjustment for PTH.
Model 4: All endocrine and inflammatory markers in model, adjustment for all confounders.

Additional analyses of number of frailty indicators

From cross-sectional analyses (Table 4, left segment), it can be seen that low serum concentrations of 25(OH)D were associated with three and four or more frailty indicators (Figure 1). Moderate levels of serum 25(OH)D were associated with three frailty indicators only. Low serum IGF-1 was associated with four or more frailty markers.

From the prospective multinomial logistic regression analyses (Table 4, right segment), it can be seen that low serum 25(OH)D was associated with one and three or more frailty indicators (Figure 1). Furthermore, moderately elevated serum CRP was associated with three or more frailty indicators. The results did not change when all serum markers were adjusted for each other (results not shown).

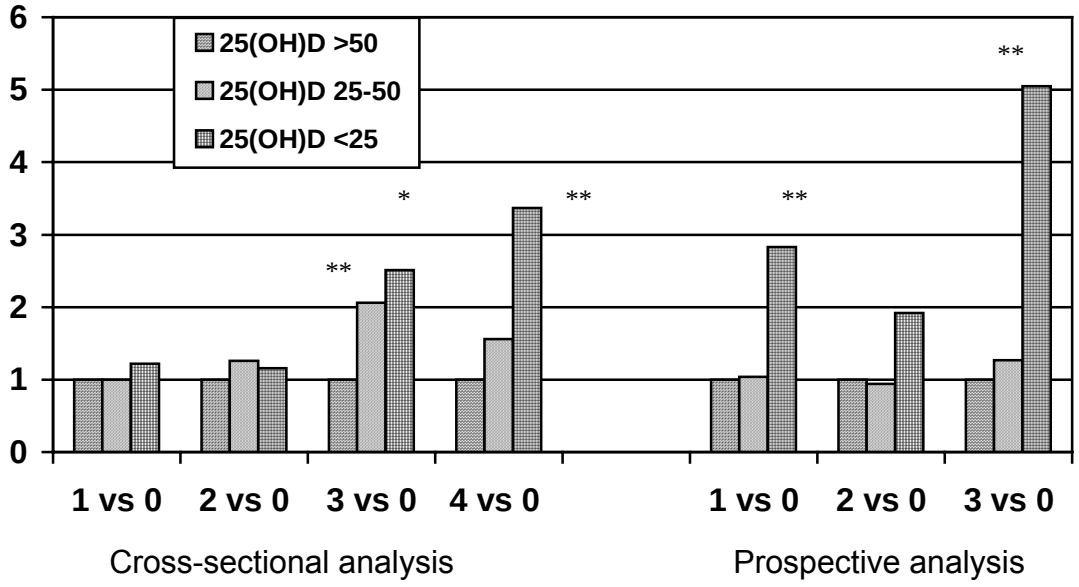

Figure 1. Odds ratios from multinomial logistic regression analyses of the association between 25(OH)D and frailty.

The group with 25(OH)D >50 nmol/l is the reference group.
*P<. 05, ** P<. 01
Adjustment for age, sex, education, number of frailty indicators present at baseline, smoking status, alcohol consumption, use of anti-inflammatory drugs (IL-6 and CRP), use of estrogen (IL-6 and CRP), obesity (IL-6 and CRP), physical activity (IL-6 and CRP), season of blood sampling (25(OH)D), PTH (25(OH)D), and the self-reported chronic diseases: cardiac disease, peripheral arterial disease, diabetes mellitus, arthritic disease

Table 4. Odds Ratio's (with 95%CI) from multinomial logistic regression analysis of the association of single serum markers and the number of frailty indicators cross-sectionally (N=1271) and prospectively (N=885).

Number of frailty indicators	Cross-sectionally 1 vs. 0*	Cross-sectionally 2 vs. 0*	Cross-sectionally 3 vs. 0*	Cross-sectionally ≥ 4 vs. 0*	Prospectively 1 vs. 0 **	Prospectively 2 vs. 0 **	Prospectively ≥3 vs. 0 **
IL-6 <5 pg/ml	1	1	1	1	1	1	1
IL-6 ≥5 pg/ml	0.97 (0.60-1.56)	0.99 (0.58-1.70)	1.10 (0.58-2.14)	0.73 (0.33-1.61)	1.28 (0.70-2.34)	0.90 (0.42-1.91)	1.11 (0.48-2.53)
CRP <3 ug/ml	1	1	1	1	1	1	1
CRP 3.0-10.0 ug/ml	0.84 (0.58-1.13)	0.98 (0.67-1.44)	1.30 (0.81-2.09)	0.83 (0.48-1.43)	1.17 (0.79-1.73)	0.98 (0.60-1.59)	**1.88 (1.08-3.26)**
CRP >10 ug/ml	0.64 (0.40-1.01)	0.84 (0.51-1.38)	0.88 (0.46-1.69)	1.28 (0.67-2.44)	0.94 (0.54-1.64)	1.08 (0.56-2.08)	1.10 (0.48-2.52)
25(OH)D <25 nmol/l	1.22 (0.66-2.24)	1.16 (0.59-2.26)	**2.51 (1.19-5.30)**	**3.37 (1.56-7.29)**	**2.83 (1.17-6.84)**	1.92 (0.70-5.23)	**5.05 (1.80-14.14)**
25(OH)D 25-50 nmol/l	1.00 (0.71-1.40)	1.26 (0.86-1.84)	**2.06 (1.25-3.41)**	1.56 (0.88-2.79)	1.04 (0.70-1.54)	0.94 (0.58-1.50)	1.27 (0.73-2.24)
25(OH)D >50 nmol/l	1	1	1	1	1	1	1
IGF-1 ≤ 7.7 nmol/l	1.58 (0.91-2.76)	1.52 (0.83-2.80)	0.96 (0.44-2.07)	**2.15 (1.05-4.42)**	1.29 (0.65-2.56)	1.07 (0.49-2.35)	1.72 (0.76-3.92)
IGF-1 >7.7 nmol/l	1	1	1	1	1	1	1

In bold P< .05.

* Adjustment for age and sex education, smoking status, alcohol consumption, use of anti-inflammatory drugs (IL-6 and CRP), use of estrogen (IL-6 and CRP), obesity (IL-6 and CRP), physical activity (IL-6 and CRP), season of blood sampling (25(OH)D), PTH (25(OH)D), and the self-reported chronic diseases: Cardiac disease, peripheral arterial disease, diabetes mellitus, arthritic disease, chronic obstructive pulmonary disease, stroke and cancer.

** Adjustment for all variables mentioned above and number of frailty indicators present at baseline.

Discussion

To our knowledge, this study is the first to examine the association of four endocrine and inflammatory markers with prevalent and incident frailty in a large population-based sample. Low serum concentration of 25-hydroxyvitamin D (25(OH)D) was associated with prevalent and incident frailty with a clear dose-response relation. In the prospective analyses, moderately elevated levels of CRP (3.0-10.0 ug/ml) predicted the incidence of frailty. These associations were independent of each other and independent of the effects of smoking, drinking, high BMI, intense physical activity, use of anti-inflammatory drugs, chronic diseases and education.

The mechanism explaining the relation between low levels of 25(OH)D and frailty is not yet clear. Low 25(OH)D levels have been shown to be associated with low muscle strength, falls and disability (13;16). In a previous report based on LASA, low 25(OH)D levels were found to be associated with sarcopenia (15), showing that both vitamin D deficiency and insufficiency may cause loss of muscle mass and strength. As a result of loss of muscle mass and muscle weakness, older persons may become less active, accelerating the frailty process. A reversed pathway is also possible: older persons often may not go outside and may be physically inactive as a consequence of their frail health, resulting in very low sunlight exposure which subsequently causes vitamin D deficiency. However, this pathway is not supported by our longitudinal analyses. Thus, the first pathway seems the most likely. Although the Longitudinal Aging Study Amsterdam is a prospective cohort study. As in most prospective cohort studies, it remains difficult to investigate causal relationships. Randomized clinical trials are necessary to investigate whether vitamin D supplementation can prevent frailty. It is known that a low serum 25(OH)D concentration can be easily corrected by sunlight exposure or vitamin D supplementation of 400-800 IU/day. Supplementation has been shown to effectively improve vitamin D status, bone mineral density and muscle strength in older persons (13;16). However, no trails have been performed focusing on new frailty.

In the only other large cross-sectional study investigating the relation between frailty and biological serum markers, Walston et al. found that persons who had CRP levels >5.77 mg/l had an OR of 3.5 for prevalent frailty, in contrast to our study which showed no association between CRP and prevalent frailty (19). However, in our

study, moderately elevated levels of CRP (3-10 µg/ml) were associated with incident frailty in both men and women after three years. With aging, the levels of circulating cytokines increase, equivalent to a low-grade systemic inflammation, but not necessarily to the levels of acute infections (17). CRP levels above 10 µg/ml are generally associated with acute disease. This is supported by our data: the respondents with the highest CRP levels had more chronic diseases, used more anti-inflammatory drugs, had more frailty indicators present at baseline and were more often lost to follow-up (data not shown). High CRP levels have been shown to be associated with a high risk of cardiovascular events and mortality (37). A possible explanation why we did not find an association with frailty in subjects with high levels of CRP, but only in subjects with moderately elevated levels of CRP, is selective dropout. Nevertheless, the finding that moderately elevated levels of CRP are associated with incident frailty is in agreement with the hypothesis that frailty is a result of chronic low-grade inflammation.

In this study low serum IGF-1 was significantly associated with the presence of four or more frailty indicators in cross-sectional multinomial regression analysis. In logistic regression analysis, a tendency for an association between low IGF-1 and frailty was seen. This finding is in line with reports that IGF-1 is associated with disability and mobility decline (8;36).

In contrast to other studies in which the association between IL-6 and frailty was examined (20;21), we found no association between IL-6 and frailty. A possible explanation for this lack of association is the high detection limit of our assay. Associations between IL-6 and health outcomes have been observed at levels far below the detection limit of our study (22;34).

Leng et al. found an inverse relation between IL-6 and IGF-1, suggesting an interaction between endocrine and immune functioning (21). IL-6 plays an important role in the inflammatory response by inducing the synthesis of acute-phase proteins, such as CRP, and inhibiting the synthesis of IGF-1 (39). In this study, we found no interaction between Il-6 and IGF-1. However, this could be the result of the high detection limit for IL-6, limiting the number of respondents in which the interaction could be examined. Results from other studies have shown that vitamin D has important effects on the function of the immune system (40). Vitamin D deficiency has been shown to occur in patients with inflammatory bowel disease (41) and vitamin D status was associated with cancer and autoimmune diseases (42). Studies

in mice have shown that supplementation with vitamin D can protect mice against developing insulin-dependent diabetes mellitus (43;44). More research is needed to study the functional relationship between the endocrine and immune system in humans to gain more insight into the development of frailty.

In this study and in other studies, a low BMI and a low physical activity score were used as frailty indicators. The analyses were adjusted for high intensity physical activity and a high BMI. This procedure might have led to over-adjustment, because physical activity has been shown to be associated with lower inflammation levels (31;34;45), as opposed to obesity, which is associated with greater inflammation (33). However, the associations did not change when not adjusting for these factors. Of interest is our finding that those who were frail at baseline were more often obese than the non-frail. Moreover, those who became frail were more often obese than to those who did not become frail. These results suggest that perhaps the concept of frailty needs to be adjusted. Possibly, not only low body weight but also obesity should be included as a frailty indicator. Obesity increases the risk of arteriosclerosis and cardiovascular disease, which both have been suggested as possible pathways leading to frailty (46). The role of the potentially u-shaped relation between BMI and frailty should be examined in future studies.

Recent studies showed potential benefit of physical activity with regard to the levels of inflammatory markers, as physical activity was associated with lower levels of inflammation (12;34;45). Physical inactivity is also an important contributor to the development of frailty and loss of muscle mass. In addition to observational studies, trials are necessary to investigate the effect of physical activity on inflammation. So far, to our knowledge no trials have been performed on the direct relation between physical activity and serum inflammatory markers.

The presence of seven self-reported chronic diseases was studied as a potential mediator of the relation between the serum endocrine and inflammatory markers and frailty. The chronic diseases included in this study were chronic obstructive pulmonary disease, diabetes mellitus, arthritic diseases, peripheral arterial disease, cardiac diseases, cancer and stroke. These chronic diseases are characterized by increased inflammation. Chronic diseases are also related to frailty (1). However, no mediating effect of these diseases on the association between the serum markers and frailty could be demonstrated. This suggests that the serum markers examined had an independent effect on prevalent and incident frailty.

However, it remains possible that other chronic diseases, not included in this study, are mediators in the relation, leading to an overestimation of the effect of the serum markers.

A further limitation of this study is the relatively long follow-up interval of three years and the determination of the biological serum markers at baseline only. Frailty is conceived to be a dynamic process and therefore multiple assessments of frailty and the biological serum markers using short time intervals might have shown more precisely the effect of biological serum markers on the development of frailty (7).

In conclusion, this study shows that low serum 25(OH)D concentrations are associated with prevalent and incident frailty. The respondents with moderately elevated serum CRP were at risk of becoming frail after three years. No consistent associations were observed for IL-6 and IGF-1.

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Chapter 6

What does Quality of Life mean to older frail and non-frail community-dwelling adults?

Submitted as: M.T.E. Puts, N. Shekary, G. Widdershoven, J. Heldens, P. Lips, D.J.H. Deeg. What does Quality of Life mean to older frail and non-frail community-dwelling adults?

Abstract

Quality of life is a commonly used but seldom defined concept and there is no consensus on how to define it. The aim of this study is to explore the meaning of quality of life to older persons living in the community and whether important aspects of quality of life differ between frail and non-frail older adults. Qualitative interviews were conducted with 25 older men and women. The audio-taped interviews were transcribed and coded for content and analyzed using the grounded-theory approach. Five themes emerged: (physical) health, psychological well-being, social contacts, activities, and home and neighborhood. Having good medical care, finances and a car emerged as conditions for good quality of life. Respondents compared themselves mostly to others whose situation was worse than their own, which resulted in a perceived satisfactory quality of life. No differences were found between frail persons and non-frail persons in the importance of these themes. However, the health of the frail limited the amount and scope of activities that they performed. In sum, as frailty increased, quality of life was observed to decrease and the priorities of the domains of quality of life were observed to change.

Introduction

Quality of life is a commonly used but seldom defined concept (1), and there is little agreement about what the term describes (2). It is defined by the World Health Organization (WHO) as “an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns”. The WHO considers it as a broad-ranging concept affected by the person’s physical health, psychological state, level of independence, social relationships, and relationships with salient features of their environment (3). Moreover, it is a difficult construct to measure because quality of life is unique to individuals (4-6).

Carr et al. (1) described a few problems with measuring quality of life. Existing questionnaires do not take into account the expectations that affect judgments about the quality of life. Furthermore, the reference value of expectations may change over time, a phenomenon called “response shift” (1).

Several studies have shown that the areas people consider important differ by age: young persons find work and finances important, whereas older persons judge health and mobility most important (7;8). Browne et al. (9) found that the relevance of domains in an individual’s of quality of life was likely to change and, even when older persons could freely name domains of importance, these domains had an idiosyncratic meaning for them.

There is little information about the meaning of quality of life to older persons (10;11). Bowling (12), Fry (6) and Xavier et al. (13) suggested that the concept of quality of life and its quantitative measurement stems mostly from experts as opposed to lay views. Most questionnaires have been developed for younger people or specific patient groups and may not include aspects that are important for older persons (12). In a recent review of instruments designed to measure quality of life, it was concluded that there is a lack of consensus over which instrument to use and that only three instruments were developed with the involvement of older persons (13).

There have been a few qualitative studies on the meaning of quality of life for older persons. These studies have shown that social relationships, social roles and

activities and health, psychological outlook and well-being, home and neighborhood, finances and independence are important measures of quality of life (10;14-18).

An increasing number of older people will become frail as the number of older persons continues to grow. Frailty is often used to describe a state in which older persons are in a delicate balance at risk for many adverse outcomes such as falls, disability, institutionalization and death (19). No study has examined whether quality of life has a different meaning for frail older adults than for non-frail older adults. The aim of this study is to describe the meaning of quality of life from the perspective of older community-dwelling persons in the Netherlands and to examine whether there are differences between frail and non-frail individuals.

Methods

Study Sample

The data were collected in the context of the Longitudinal Aging Study Amsterdam (LASA). This is an ongoing multidisciplinary study on predictors and consequences of changes in physical, cognitive, emotional and social functioning in older people in the Netherlands. A random sample of people aged 55 to 85 was drawn from population registers of eleven municipalities in three geographical areas in the Netherlands in 1992. The details of the LASA study have been described elsewhere (20;21) (http://ssg.scw.vu.nl/lasa/). The Medical Ethics Committee of the VU University Medical Center approved the study, and informed consent was obtained from all respondents.

This study included respondents in Amsterdam and the vicinity who participated in face-to-face interviews in 2001/2002 and completed a postal questionnaire in 2004. Respondents with low cognitive functioning or who were institutionalized in 2001/2002 (MMSE<24 (22)) were excluded. A theoretical sample was used (23;24) to obtain informants with backgrounds as varied as possible with regard to age, sex and frailty status in order to facilitate maximum information. Respondents were selected from those who had complete data in 2001/2002 on eight frailty markers: low body-mass index, low peak expiratory flow, poor vision and hearing ability, incontinence, low sense of mastery, suffering from depressive symptoms and physical inactivity. The selected respondents were either frail (defined

as having three or more out of the eight frailty markers present (25)) or non-frail (defined as having no frailty markers present). Thirty-two respondents were selected for this study, out of whom four frail respondents refused, one frail person could not be contacted, one non-frail respondent had no time for an interview, and one frail respondent was excluded after the interview due to severe cognitive impairments, resulting in twenty-five older persons participating.

Data collection and analysis

A semi-structured interview was carried out with a topic guide in the home of the respondents and audio taped. Interviews lasted approximately one hour and a half and were conducted by two researchers (MP & NS). The total number of interviews was guided by saturation. Each interview covered the following topics: (1) important themes related to quality of life at this moment, (2) selection of the most important theme for quality of life, (3) appraisal of the quality of life at this moment and reasons for this appraisal, and (4) conditions for maintaining good quality of life when aging.

Mind mapping was used during the interviews as a memory aid to visualize what the respondent had said. MP and NS wrote down the themes mentioned by the respondent on small notes, which were then laid out on another paper so the respondent could see the themes he or she mentioned, thus providing an overview of all themes mentioned during the interview.

Transcription was carried out to a level that included words, speech particles, and pauses (untimed). Data were analyzed using the grounded-theory approach, in which a theory is derived by the constant comparative method from data that have been systematically gathered and analyzed through the research process (24;26). Data analysis was supported by Kwalitan software (27). The first step in the analysis was open coding. Researchers MP and NS read the transcriptions several times to explore any emerging themes. Codes were then added to the transcripts. Both MP and NS coded all interviews independently; the codes for each transcript were then compared and discussed until a consensus was reached. In the second phase of coding (axial coding), categories and subcategories of quality of life were defined and integrated according to their relationships. These links were explored in further transcripts. GW, JH and DD read some transcripts to discuss main and subcategories. The third step (selective coding) was used to achieve completeness, meaning that as many of the variations were explained with as few categories as

possible. A coding manual was made to list the codes and their definitions and was discussed with the other authors and modified when necessary. The process of defining and refining themes and coding the transcripts was continuous throughout the analysis. MP and NS compared the list of themes that respondents felt to be important to quality of life for frail and non-frail persons and any differences noted were discussed with all other authors.

Results

Fourteen respondents were non-frail and eleven respondents were frail (Table 1). There were fourteen men and eleven women; the mean age was 78.7 years (range 67-90). Both the frail and non-frail suffered from chronic diseases, but the frail had, on average, more chronic diseases than the non-frail. In Table 1, the appraisal of quality of life is presented.

First, the important themes will be described, then the differences between the frail and non-frail with regard to themes important for quality of life. Five main categories for the meaning of quality of life (QoL) emerged: (physical) health, psychological well-being, social contacts, activities, and home and neighborhood (see Table 2 for a description of the themes and dimensions). All the themes were felt to influence other themes. Factors, which the respondents that positively and negatively contributed to the themes of quality of life, are described below.

(Physical) Health

Health is needed to stay independent. Good medical care, medications, walking aids (like rolling walkers), self-chosen initiatives for maintaining health (such as a healthy diet), taking care of oneself and being able to exercise contributed to good QoL. Having sufficient money to buy medical aids and medications and having a car to drive to the hospital or shops when the respondents were not able to walk also contributed to good QoL. Health problems such as chronic diseases decreased QoL substantially.

Table 1. Characteristics of the study Sample.

	Total sample N=25	Non-frail N=14	Frail N=11
Age mean (SD)	78.7 (5.9)	79.0 (6.8)	78.8 (4.8)
Range	(67.2-90.6)	(67.2-90.6)	(69.6-84.8)
Sex			
Men	14	8	6
Women	11	6	5
Level of education			
Low	9	5	4
Middle	10	6	4
High	6	3	3
Marital Status*			
Never married	3	0	3
Married	16	10	6
Divorced	1	1	0
Widowed	5	3	2
Frailty markers*			
Low BMI[#] (<23)	4	0	4
Low peak flow	4	0	4
Vision problems	1	0	1
Hearing problems	6	0	6
Incontinence	8	0	8
Low mastery	7	0	7
Depression	5	0	5
Low physical activity	3	0	3
Chronic Diseases*			
Range	(0-5)	(0-3)	(0-5)
COPD[#]	7	3	4
Cardiac diseases	7	5	2
PAD[#]	9	5	4
Diabetes	2	0	2
Stroke	5	2	3
Rheumatic complaints	18	8	10
Cancer	6	3	3
Appraisal own quality of life			
Good	16	12	4
Satisfactory	6	2	4
Unsatisfactory	3		3

* The information is from the last interview in 2001/2002.

[#] BMI=Body Mass Index, COPD=Chronic Obstructive Pulmonary Disease, PAD=Peripheral Arterial Disease

Psychological well-being

Most respondents were very optimistic, had a positive outlook. Those who did not accept their declining health were less satisfied with their QoL. Both frail and non-frail persons found well-being very important for QoL. The psychological well-being of frail persons was negatively affected by health and social problems.

Having good contacts with partner, family and friends, staying busy and being informed about what happens in the world, watching the news and performing new activities has a positive effect on QoL. Furthermore, learning new things and continuing to study when growing older contributed positively to psychological well-being.

However, there are also problems that negatively affected psychological well-being, such as worries about the health of the partner or important others. About half of the respondents mentioned concerns about the medical examination for their drivers' license and fear of losing this; having a drivers' license gave a feeling of freedom. Anxiety, such as fear of complications of a disease or treatment (for example, in a former cancer patient, uncertainty as to whether the cancer would return), negatively affected QoL.

Social contacts with partner, family, friends and neighbors

A difference was observed in social contacts between those living alone and those who lived with their partner. Those with a partner had a larger social network. Nevertheless, most activities were performed with the partner, and the other contacts were less intense. Those who had lost their partner and lived alone reported missing their partner; they missed having somebody to talk to about everyday activities and things that worried them. They did not want to burden their children with their troubles because they felt that their children had a life of their own.

The respondents without a partner sometimes felt lonely. Respondents without a partner more often had a smaller social network but more intense contacts with these persons. Respondents with a partner pitied those without one because they were alone, and felt some responsibility to check on them regularly. About half of the respondents lived in an apartment building for seniors in which activities such as drinking coffee together were organized and this was highly valued. Having enough money to be able to afford a car to go visit family and friends, and being able to

afford a computer and telephone when other forms of social contact were limited by health problems, facilitated social contacts.

The health problems of the respondents or their partner negatively affected social contact. Death or dementia of friends and family reduced the social network and decreased social contacts. Not being able to drive the car had a negative impact on social contact, especially if the partner lost the ability to drive and respondents became dependent on other persons to take them places. Frail respondents mentioned that using public transportation was difficult because of their own health problems or those of their partners.

Activities to enjoy, relax, socialize, maintain health, and activities to help others

The healthy non-frail respondents were very active outside the house. The frail respondents with health problems reported less intense activities. They read more books, watched television, often used a computer and made wooden ships, bird houses, etc., and stayed closer to the house or inside the house. The respondents living alone more often enjoyed social activities like going to card clubs or activities organized in the senior apartment buildings, whereas respondents with partners did not go to such activities as often.

Having enough money, a car to go out, family members who organize activities, recreation areas in the neighborhood, organizations like the Red Cross for activities and holidays for the disabled, made activities more diverse. Health problems limited activities, as did feeling down and not having sufficient money.

Home and neighborhood

The home and neighborhood were important in two different ways. First, the facilities that were present in the neighborhood (such as grocery stores) and the house of the respondent (the amount of space, an elevator, an alarm system, adjustments in the house) were mentioned as important.

Second, the perception of the neighborhood by the respondent: the feeling of safety in the neighborhood, especially after dark, was mentioned as important. About half of the respondents found living in a quiet neighborhood very important. Some respondents in rental apartments were uncertain whether they could remain in their home because of renovation plans. They did not know yet whether it was possible to return, and worried about an increase in rent after the renovation. Living in a

neighborhood where there were drugs and a lot of noise substantially decreased QoL. Respondents using a rolling walker complained that the sidewalks were too small and filled with bicycles, tree trunks, and other obstacles, making it difficult to walk without stumbling over something.

Differences between frail and non-frail persons

The main themes that were felt as important for quality of life for older persons did not differ between the frail and non-frail respondents. However, the health of frail respondents limited the scope of their activities; they tended to stay close to home and did not go as far from the house on holidays, or they did not go on holiday at all anymore, while those in good health still did. In addition, frail respondents named social contacts as the most important factor for quality of life, while the non-frail in good health reported health as the most important.

All respondents were asked to rate their quality of life. Twenty-two said that it was satisfactory to good and three reported their quality of life as poor. On average, frail respondents reported a lower quality of life than non-frail respondents. While most frail respondents had accepted their poorer health and adjusted their activities accordingly, poorer health caused the frail to report their quality of life as lower, on average, than the non-frail.

Discussion

Health, well-being and social contacts were the more important factors in regard to quality of life. Apparently, the simple things in everyday life, such as having somebody to talk to and being able to perform activities that one liked, were very important for quality of life. If these things were possible, older adults were more likely to rate their quality of life as satisfactory. Persons who fulfilled the criteria of our frailty definition rated a lower quality of life on average than the non-frail persons.

Some remarkable findings were the expectations the respondents had about their health and well-being. Our respondents had clear ideas about the point in their future when their lives would no longer be worth living. At that point, they stated that they would prefer to die. A similar finding was reported from the studies of Fry (6) and Borglin et al. (10). In another study using the time trade-off technique among older

women, eighty percent reported that they would rather be dead than experience a loss of independence and subsequent admission to a nursing home, e.g. after a hip fracture (28). Almost all respondents worried about dementia and admittance to a nursing home. This greatly influenced their perception of quality of life, an observation that, to our knowledge, has not been mentioned in other studies.

The older adults in our study compared aspects of their quality of life with those of others. Beaumont and Kenealy (29) postulated that a downward comparison strategy might promote a higher perceived quality of life. Frieswijk et al. (30) found that mildly frail elderly persons identified themselves with a downward comparison target and that the most frail persons identified themselves with somebody doing better, which is in line with our observation that the three frail persons in our study rated their quality of life as unsatisfactory and compared themselves with somebody who was doing better than they were.

Quality of life was described as a dynamic construct influenced by adaptation, coping, self-control, uncertainty, expectations and optimism by Allison et al. (31). In our study, respondents mentioned that adaptation was very important to maintain quality of life. When health was poor, there was a shift from health to social contacts as the most important aspect. However, the effect of poor health appeared to be something that not could be completely accepted or adjusted to, resulting in a still satisfactory, but less often good, quality of life.

In this study, social activities as helping others were very important for a good QoL. Leung et al. (32) found in elderly Chinese that social activity and service as a quality of life domain was important. Bryant et al. (33) found that healthy aging meant doing something meaningful. Similar to our results, Bowling et al. (14) and Gabriel & Bowling (16) found that home and neighborhood were important for QoL. In addition, they reported that the main factors that negatively affected quality of life were a poor home and neighborhood, poor health and poor relationships. Social activities such as helping others and home & neighborhood should be included as domain of quality of life in future studies.

Farquhar (12) found that family and activities were mentioned most in relation to quality of life in older old people. In contrast, health was more often mentioned in contributing to quality of life in the younger old than in the older old. However, Farquhar did not consider health status. Older old persons are more likely to be frail. Other studies have not examined whether the themes important to quality of life differ

between frail and non-frail persons. In this study, frail persons-those with more health problems- found social contacts more important, while the non-frail found health most important. Moreover, there was a difference in regard to the people with whom social contacts were maintained.

In summary, existing instruments for measuring quality of life may not be valid for older persons since they do not capture all the themes mentioned by older persons. Our study showed that quality of life consists of more than health and functional capacity. Another study showed a difference between the concepts of QoL and health status (34). Instruments designed to measure the quality of life for older persons should take into account more aspects that cover social functioning, expectations regarding future health, well-being and quality of life, feelings of safety, and living conditions.

Quality-of-life measures can be used by health-care professionals to identify and prioritize problems, facilitate communication, screen for hidden problems, facilitate shared clinical decision making and monitor reactions to treatment (35). Because care is provided to maintain or improve quality of life, health-care professionals should discuss with care recipients what is important to them in relation to quality of life as it varies among older adults according to their expectations and experiences.

One limitation of this study, as in all qualitative studies, is the risk of subjectivity. To reduce this risk, two researchers coded the transcripts, and the emerging themes were discussed with the other authors. In addition, quotations from the interviews are provided to enable the reader to judge the credibility of our findings (see Table 2). Our study is based on a small sample of respondents in Amsterdam and its vicinity and cannot be generalized to other populations. A final limitation is that this study included frail and non-frail persons based on the last measurement cycle of LASA in 2001/2002. To create as great a contrast as possible, the group of non-frail persons was defined as having none of the frailty markers in 2001/2002. Because the health of respondents is likely to have deteriorated since that time, the non-frail group was very likely to have one or two frailty markers present at the time of the interview, but the development of three or more frailty markers was not likely.

In conclusion, for the older adults in our study, quality of life included being in good health, feeling good, having social relationships, being active, helping other people and living in a nice house in a good neighborhood. As frailty increased, quality

of life was observed to decrease and the priorities of the domains of quality of life were observed to change.

Table 2. Domains and subcategories of quality of life.

Main categories	Subcategories	Examples
1. (Physical) Health	***Health status*** To be independent, it is necessary to be in good health according to many respondents.	**Woman, 77 years old, not frail, living alone** Health. Well, yes, that is the most important, that one is healthy. Yes, because if you're healthy, then most of the time you are in a good mood and are capable of meeting other people and I mean that, yes, then you are able to go out and that's what matters the most. **Man, 78 years old, not frail, living in senior apartment building** I (Interviewer) Hmm. You wrote down good health, no financial worries, and recreational activities like city trips and social contacts. R (Respondent) Yes. I What does good health for you, exactly? R Well, that you can move with the help of medical aids and, well, everything diminishes with aging because you lose your limberness, but, well, uh, that you're independent in daily activities such as bathing, getting dressed, shopping, these are the kinds of things I mean. **Woman, 69 years old, frail, living with partner in senior apartment building** Quality of life. Well, that is health and because of my eye (points at her eye), I don't see so well with this eye. **Woman, 69 years old, not frail, living with partner in senior apartment building** And hoping that your are healthy. At least as much is possible when you are aging, because, well, my husband had always worked until he turned 65. He hasn't been retired long, but now he has cardiac arrhythmias and that's very annoying because you can't do what you want to do. Well, yes, at least I am more worried about it than he is, because now we cannot go places like on vacation. I don't dare because I don't drive, so then your are always stuck here.
	Expectations regarding health: ***-Comparison with health at younger ages*** ***-Comparison with health of others: parents, friends and others*** Expectations regarding health in old age had an important influence on the respondents' appreciation of health. The respondents frequently compared their health to earlier times. Some respondents had been very ill in the past and had low expectations of health in old age, but now their conditions were better managed. Most respondents compared themselves to others, mostly negative comparisons with their own parents and other family or friends. Respondents reported the level of independence of their parents in old age; they compared themselves to that level and found themselves in better health and functioning better.	**Man, 84 years old, frail, living with partner in senior apartment building, has several chronic diseases and was very ill when he was young** R (respondent): Yes. Every now and then you have a problem; it's not as good as it could be but that doesn't bother me at all. I (Interviewer): Your health problems? R: Well, now that you are older and you know that in advance and if you remember what it used to be like, well then I would have to say that I have done pretty well! Because I can still hear the doctors saying to my wife that I would be lucky to live to be 37, 38 years old and then it would be over. Well, I'll be 85 in May this year, so I can't complain. **Man, 81 years old, not frail, living with partner, suffering from asthma** R: Well, it's sad, of course. And when you see people around you who are getting older and suffering, well this person is going blind and deaf and things like that, that person has to be in a wheelchair. Well, you can't do anything about it, but I don't want to . . . um. . . . I: That would not have any quality of life for you any more? R: Well, no, definitely not…If I had to be in a wheelchair and couldn't do anything at all any more, well I say go ahead and kill me.

1. (Physical) Health	***Genes*** Genes were frequently mentioned as important to health and ascribed to good or bad luck.	**Man, 67 years old, not frail, living with partner** Well, quality of life is, in any case, health. So, if you do not have health problems, well then you are blessed and you're thrilled with that, but in the end, it is not something you can be proud of because it is not something that you did! You did do it in the sense that you can say you lived a healthy lifestyle but what I mean is, it's your genes that cause health problems. That is just luck!
2. Psychological well-being	***Psychological well-being*** Feeling good was very important according to most respondents.	**Man, 75 years old, frail, living in senior apartment building** Well, if you feel good, you can meet people and then you feel even better. **Woman, 74 years old, frail, living with partner, involved in legal battle to see her grandson.** Well, I feel very angry and tremendously sad, and a lot of the time I feel helpless. We have good support but, well, these people can only do their best and not more. But growing older this way is not nice! Because we need help all the time, we get that from an ambulant mental health team. **Man, 75 years old, not frail, living with partner** Well, I am happy. I am a cheerful person and I enjoy working, sleeping, and working. **Woman, 81 years old, frail, living alone** Well, health and that you enjoy the work you've had. That you might continue working after your retirement and uh I had a profession and when I officially retired from the academy of music, well, afterwards I continued to teach a woman violist that a colleague of mine in Germany referred to me and another girl from Korea, and it was fun to continue working. I mean, you could say that my profession has always been my hobby and so you spend all your time and energy on that, and maybe that's what keeps you energetic (laughs). That I play for myself.
	Expectations regarding psychological well-being: ***-Comparison with parents*** ***-Comparison with others such as friends, family and neighbors*** Expectations regarding psychological well-being substantially influenced the appreciation of own QoL; the respondents compared their situation to their parents' situation and that of other significant persons in the environment. Respondents were more fearful of dementia if one of the parents had suffered from dementia; some respondents had taken care of the parent with dementia for a long time.	**Woman, 69 years old, not frail, living with partner in senior apartment building** I feel terrible about that. Because if you . . . uh. . . if you suffer from dementia and you start doing weird things . . . I always say if I am suffering from dementia, for God's sake give me something. Yes, I am very afraid of dementia, that you . . . that your mother's had it. Fortunately, we (my sisters and I) haven't had a problem with it yet but it can, of course, always happen that you think . . . . Well, you forget something. That happens to everybody . . . that you walk to the kitchen and think oh god! But my sisters say the same thing. **Woman, 74 years old, frail, living with partner** Actually, yes, because you still want to do so much but can't any more! And when you look around and see older people who are much older who can still do things, then . . . um . . . well, you can't really say it's jealousy and you can't do anything about it, of course, but you think to yourself, why them and not me?
	Coping/Acceptance The way respondents coped with health problems affected how they felt; acceptance of health problems, adjusting to declining health, adjusting activities, and staying optimistic was mentioned as important to QoL. Accepting that health declines and finding ways to adjust activities and expectations was most important to maintaining a satisfactory quality of life.	**Man, 67 years old, not frail, living with partner, has severe vision problems** Well, the transition is very hard! You have to learn to live with the fact that your eyesight keeps getting worse and that you are becoming more dependent, and that you . . . um . . . then your wife is having problems because you have trouble understanding each other and it's hard to talk about, how to tell her without hurting her feelings. For example, if somebody says to me, "It's over there," I don't know where "there" is. That's only one little thing and there are a lot like that, so we both have to learn to communicate better and, well, that's very difficult.

2. Psychological well-being	***Coping/Acceptance***	**Man, 78 years old, not frail, living in senior apartment building** Yes, because I am hampered by my heart condition but I can still do things I want to do well enough. But sometimes . . . um . . . you want to do more that you should and then . . . um . . . I am sensible enough to know not to push myself, but you think to yourself I would love to do that, but, well, that's not possible. But I am quite satisfied because I know people that have also suffered from a heart attack and, well, they are sitting around waiting to die. Well, that is something I don't think about. This Sunday I turn 79 but I don't feel 79! **Man, 76 years old, frail, living with partner** As long as you can appreciate what you have and what you are able to do, life is enjoyable! But if you can't appreciate it anymore, then you have to say that you, um, are not satisfied any longer, it has no meaning anymore. **Woman, 81 years old, frail, living alone** Well, yes, as you age, you can't move as much. Everything happens more slowly. That happens automatically, adjusting to your situation. You adjust automatically to getting older.
	Future psychological well-being Almost all respondents feared dementia and nursing homes. In addition, people who were volunteers who had seen nursing homes from the inside or respondents who had been visitors in nursing homes did not want to live there.	**Woman, not frail, 90 years, living with her daughter, volunteered 5 days a week in a psychogeriatric nursing home and in a residential home** When I see those poor people sitting in a chair all day, who don't go anywhere except when they're taken to the toilet, and if you have the kindness to take the wheelchair and take them for a walk around the house or, in the summer, outside in the garden…well that's it. Then I think I don't want to grow old like that. I would love to live to be 100, but not in that way. Not in that way.
	Character/childhood Character, youth and childhood were often mentioned as reasons for keeping a strong spirit while aging; It was important to keep on fighting; QoL was something to fight for.	**Man, 81 years old, not frail, living with partner** Yes, always, my whole life. Well, maybe it's a result of the war (Second World War) and all that. I mean I have always traveled a lot but when I was 17, I was captured and had to do forced labor in Germany, and, after that, you never really have peace of mind again. Then I was . . . um . . . the four of us emigrated to New Zealand. Well, I've always been an enterprising person. I was a carpenter and then I joined the fire-brigade, and then I left and joined the fire brigade again. Well, I've had a very varied life.
	Religion Religion gave respondents hope and strength	**Woman, 74 years old, frail, living with partner** Yes, my faith. That keeps us going. We are Jehovah's witnesses and that really keeps us going! We receive a lot of support from fellow believers and each other and that is great. For our party we invited family and friends and half of them were fellow believers, and everybody got along so nicely that both groups said, "Gosh. Isn't it great that everybody is so congenial".
3. Social contacts	***Contacts with partner, children, brothers, sisters, neighbors, etc.*** Social contacts had a profound positive affect on QoL. To have somebody to talk to about everyday activities and concerns contributed positively to QoL.	**Man, 81 years old, frail, living with partner** Hmm. I have a nice house and a good wife. Yes, my wife is very good. She is everything, actually. **Man, 67 years old, not frail, living with partner** Yes. No. How can I put this? The older you get, the more you focus on your own family and your children. At any rate, I have one daughter and I focus more on her and try to be there as much as possible for my daughter and grandchild. And my wife, naturally you try to share all the joys as much as possible. Yes, you are there for each other.

3. Social contacts	***Contacts with partner, children, brothers, sisters, neighbors, etc.*** **Respondents with a partner** Respondents with a partner had a larger social network, more contacts with other people but less intense contacts with persons other than their partner **Respondents without a partner** Respondents without a partner sometimes felt lonely, they had a smaller social network but more intense contacts, often lots of contact with siblings	**Woman, age 85 old, not frail, lives with partner** R Well, we do everything together. He usually does the groceries because I do not like to do the groceries so much. I find it tiresome. I only go to the greengrocer across the street. It is a nice shop and has everything. And my husband does other chores. There are some things that I am clumsy at and he does those. But we do most together and that is really straightforward. I do you find it important to have a husband to be able to do everything together? R yes! **Woman, 77 years old, not frail, lives alone** Well, if you are married; things are different, of course, when you have a husband. Now I don't, although when I was married I sometimes went on holiday without my husband [laughs], it is certainly different when you have a husband! Married life is different. Life with a husband is different from life without; if you are alone, you certainly are lonely sometimes. Yes, that is true. Despite the fact that there are many people around during the day, you have nobody you can turn to for advice. You don't want to -at least I don't want to- when I visit my children, to burden them with my worries because they have a life of their own with their own concerns, so I would never do that, but I often feel lonely. Even though I was very independent and took care of everything around the house, I miss my sounding board. You can't just ask something any more. Even though it 's been a couple of years, you still miss that. **Man, 78 years old, not frail, lives in senior apartment building** Well, yes, I have been on holiday twice this year already . . . um . . . to Egypt and to Rome, together with my oldest sister, who also lives in this apartment building. We swim together; we play cards together. So, we do a lot of things together, and that's possible.
4. Activities	***To maintain/improve health*** ***To enjoy life and relax*** ***To socialize*** ***To help others*** Respondents performed activities to maintain health; they walked often, cycled, skated, and danced and watched their diet. The respondents living alone more often enjoyed social activities, like going to card clubs or activities organized in the senior apartment buildings; respondents with partners did not go to such activities as often. About half of the respondents did some kind of volunteer work for others, especially those in better health, and one respondent still had a paid job. Some helped in nursing homes, others helped in libraries or with maintenance of the church and helping neighbors.	**Man, 81 years old, frail, lives with partner** R: Sports, walking and bicycling. I mean, I find it important, but sadly, I cannot do as much any more. I: Are you more easily fatigued, or . . .? R: Yes, but also my health is . . . um . . . last year I was on holiday and we had just arrived and I was under the shower when I heard a crack! Two vertebras had collapsed, and that was the end. I still have pain and my endurance has decreased; it is nothing like it used to be. **Man, 84 years old, frail, lives in senior apartment building with partner.** Well, you have limitations (financial). You don't hear me complaining, but there are certain things that we can't do anymore. We used to go on holiday for two weeks but now I have to choose between spending my money on a holiday or on a car. If you don't have a car, doing the shopping. . . . Well, my wife has difficulty walking and has back pain, and when we get groceries, well, she cannot make it to the end of the street! There is a grocery store just down the street, but she can't get there. **Woman, 80 years old, not frail, living with partner** Well, we have two daughters -very lovely daughters- who live close by so we see them a lot. We have grandchildren -two boys and a girl- and we also see them regularly and that's nice, too. And if there is something wrong, we help each other. These kinds of things. So, they live close by and now and then we do fun things together

4. Activities	Neighbors who suffered from illness or dementia were helped with all kind of activities. Performing activities for other people was highly valued: to mean something to others. Some respondents called it “your duty to help”. These activities ranged from driving a neighbor to the hospital to checking every morning to see if this neighbor was still alive or needed help.	**Woman, 69 years old, frail, living with partner in senior apartment building** I do volunteer work here, caring for the elderly in this apartment building. People are aging so they call on you, and then I jump in and help when they are afraid to bathe, for example, and I do sewing chores for them, and my husband is busy with maintenance jobs for them, so both of us are very busy with that.
5 House & neighborhood	***Facilities in the neighborhood and in the house*** The shops, restaurants, parking places etc. that are present in the neighborhood.	**Man, 67 years old, not frail, lives with partner, has severe vision problems** My house is very important to me now. Because my house is a tower of strength for me. [Laughs] It has become really important for me. It has always been important for me but now especially. My house is the only place where I am still my own lord and master. As soon as I leave my house, I’ll be dependent on others. So, for me, . . . um it gives you a feeling of security and makes you want to keep going in spite of losing your eyesight. So, yes, my house is very important to me! Because in my house I help with the housekeeping, I still take care of the garden, well yes, in the house I still function like a normal human being. **Man frail, 84 years, lives with partner in senior apartment building** In bygone days I used to walk to the pharmacy across the first bridge with crutches, I used to walk over there very easily with one crutch. Well nowadays, I can still walk over there easily but not back anymore. So I use a rolling walker and when I get tired I just turn around and put the brake on the rolling walker and go sit down on it. There is a seat with the school but there should be a lot more seats out there. **Women 80 years, not frail, lives with partner** Yes, we live in a nice house. We have a washing machine and a dishwasher and I am very pleased with them. Because I used to have to do all of that by hand.
	Feelings about the house and neighborhood The feelings of safety in the neighborhood, especially after dark, were mentioned as important. More than half of the respondents were afraid to go out after dark, avoided certain places, did not use public transport and did not go out alone at all after dark.	**Woman, 69 years old, frail, lives with partner** Well, certain things annoy me a lot, like the dirt in the street, what people throw in the street. Outside this building, there are two bottle banks and just look at what people throw next to the bottle banks. I clean it up at least twice a week. **Man, 81 years old, not frail, lives with partner** Well, so far, the neighborhood is not too bad, but it’s been deteriorating. That is definite. After dark, we never go out. And we never answer the door unless we are expecting somebody; otherwise, our door remains closed. After dark, we just let people ring at the door. We don’t answer. Our friends know this. . . . No, we don’t go out after dark, unless somebody picks us up with a car or something, but otherwise we don’t go out. **Man, 73 years old, not frail, living with partner** Yes, I live quite well, don’t I? It is a very quiet neighborhood with all older people. Everybody has grown old here over the years and the children have grown up and moved out. You could say that, like a normal neighborhood, it has aged, so there are all quiet people, [laughs] I suppose.

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Chapter 7

Frailty and successful aging, what do these concepts mean to older community-dwelling adults?

Submitted as: M.T.E. Puts, N. Shekary, G. Widdershoven, J. Heldens, P. Lips, D.J.H. Deeg. Frailty and successful aging, what do these concepts mean to older-community-dwelling adults?

Abstract

The aim of this study was to describe the meaning that older community-dwelling persons attach to the concepts frailty and successful aging. Twenty-five semi-structured interviews were conducted. The audio taped interviews were transcribed and coded for content and analyzed using grounded theory methods. Frailty was described as being less healthy, having walking difficulties, feeling down, being anxious, having few social contacts and not being able to do the things respondents liked to do. Successful aging was described as a process, staying healthy with good cognitive functioning, being active and having a positive outlook. Furthermore, it involved having social contacts, staying together with the partner, being able to do the things one enjoyed and having enough finances to do these things.
Existing definitions of frailty and successful aging could be adjusted to better reflect the meaning they have for older persons. Having no chronic disease as one of the criteria for successful aging should be taken less strictly, since most older persons have chronic diseases and still find themselves aging successfully.

Introduction

Successful aging and frailty are both terms that are frequently used in gerontological literature. For neither widely accepted criteria exist yet.

A frequently used definition of successful aging is that of Rowe & Kahn (1) in which successful aging exists of three components; low probability of disease and disease-related disability and absence of risk factors for disease and disability, high cognitive and physical functional capacity, and active engagement with life. Phelan & Larson (2) conducted a review of the literature and identified several definitions of successful aging. Most definitions stress the importance of maintenance of functional ability as an essential element of success. Some studies (3-5) showed that most older adults did not expect to age successfully when successful aging was defined as maintenance of high cognitive and physical functioning. It is important to know how older persons view successful aging because there is evidence that older adults with low expectations do not often believe it is important to seek health care for age-associated conditions such as declining physical health (3-6).

Several investigators (2;7-9) have suggested that very little work has been done to ascertain the views of aging individuals on successful aging. A few studies have directly assessed older adults' beliefs and attributes about successful aging (9-14). It was shown in these studies that social contact, having a sense of future, a process of adaptation, health, and happiness was important. Strawbridge et al. (15) compared the definition of Rowe & Kahn to self-rated successful aging. Fifty percent of the respondents rated themselves as aging successfully whereas only 18 percent were rated as aging successfully according to the definition of Rowe & Kahn.

The opposite of successful aging is frailty, defined as a state of reduced physiologic reserve, a diminished ability to carry out the important practical and social activities of daily living, the presence of chronic diseases, and multisystem decline (16-20). Frailty is a term used to describe a state in which older persons are at risk for adverse outcomes such as falls disability, institutionalization and mortality (20;21). The term frailty is a term often used by health care professionals and researchers. However, to date there is no study in which older adults were asked what the term means to them and how it affects their successful aging.

More insight into the perceptions by older adults of what successful aging and frailty encompasses can be useful to health care providers to help older adults to age successfully. Qualitative research may give insight into the older adults expectations' and the connections between frailty and successful aging and the relationship between both concepts. The aim of this study is to describe the meaning of the concepts of successful aging and frailty to older persons and to examine the relationship between both concepts to enhance the definition of both frailty and successful aging.

Design and methods

Study Sample

Data were collected in the context of the Longitudinal Aging Study Amsterdam (LASA). LASA is an ongoing multidisciplinary study on predictors and consequences of changes in physical, cognitive, emotional, and social functioning in older people in the Netherlands. A random sample of ages 55-85, stratified by age and gender according to expected mortality after 5 years, was drawn from population registers of eleven municipalities in three geographical areas in the Netherlands. The details of the LASA study have been described elsewhere (22;23) (see also http://ssg.scw.vu.nl/lasa/). The Medical Ethics Committee of the VU University Medical Center approved the study and informed consent was obtained from all respondents.

This study included respondents in Amsterdam and the vicinity who participated in face-to-face interviews in 2001/2002 and completed a postal questionnaire in 2004. Respondents with low cognitive functioning and respondents who were institutionalized in 2001/2002 (MMSE<24 (24)) were excluded. A theoretical sample was used (25;26) to obtain informants with backgrounds as varied as possible with regard to age, sex and frailty status in order to facilitate maximum information. Respondents were selected from those who had complete data in 2001/2002 on eight frailty markers: low body-mass index, low peak expiratory flow, poor vision and hearing ability, incontinence, low sense of mastery, suffering from depressive symptoms and physical inactivity. The selected respondents were either frail (defined as having three or more out of the eight frailty markers present (27)) or

non-frail (defined as having no frailty markers present). Thirty-two respondents were selected for this study, out of whom four frail respondents refused, one frail person could not be contacted, one non-frail respondent had no time for an interview, and one frail respondent was excluded after the interview due to severe cognitive impairments, resulting in twenty-five older persons participating.

Data collection and analysis

A semi-structured interview using a topic-guide was carried out. The interview was held at the respondents' home and audio taped. Interviews lasted approximately 90 minutes and were conducted by two researchers (MP and NS). The total number of interviews was guided by saturation. Each interview covered the areas: the meaning of successful aging and appraisal of their own aging (whether it is successful or not), the meaning of frailty and appraisal of the participants' own situation, a choice between frailty and successful aging and finally conditions to prevent frailty and positively contribute to successful aging. An equivalent of the term frailty does not exist in the Dutch language and therefore descriptions of frailty were used in Dutch (i.e. kwetsbaarheid, broosheid, fragiliteit). Transcription was carried out to a level that included words, speech particles, and pauses (untimed). Data were analyzed using the grounded-theory approach, in which a theory is derived by the constant comparative method from data that have been systematically gathered and analyzed through the research process (26;28). Data analysis was supported by Kwalitan software (29). The first step in the analysis was open coding. Researchers MP and NS read the transcriptions several times to explore any emerging themes. Codes were then added to the transcripts. Both MP and NS coded all interviews independently; the codes for each transcript were then compared and discussed until a consensus was reached. In the second phase of coding (axial coding), categories and subcategories of quality of life were defined and integrated according to their relationships. These links were explored in further transcripts. GW, JH and DD read some transcripts to discuss main and subcategories. The third step (selective coding) was used to achieve completeness, meaning that as many of the variations were explained with as few categories as possible. A coding manual was made to list the codes and their definitions and was discussed with the other authors and modified when necessary. The process of defining and refining themes and coding the transcripts was continuous throughout the analysis.

Table 1. Characteristics of the Study Sample.

Characteristics of the study Sample	Total sample N=25	Non-frail N=14	Frail N=11
Age mean (SD)	78.7 (5.9)	79.0 (6.8)	78.8 (4.8)
Range	(67.2-90.6)	(67.2-90.6)	(69.6-84.8)
Sex			
Men	14	8	6
Women	11	6	5
Level of education			
Low	9	5	4
Middle	10	6	4
High	6	3	3
Marital Status*			
Never married	3	0	3
Married	16	10	6
Divorced	1	1	0
Widowed	5	3	2
Frailty markers present*			
Low BMI	4	0	4
Low peak flow	4	0	4
Vision problems	1	0	1
Hearing problems	6	0	6
Incontinence	8	0	8
Low mastery	7	0	7
Depression	5	0	5
Low physical activity	3	0	3
Chronic diseases*		0	
Range	(0-5)	(0-3)	(0-5)
COPD#	7	3	4
Cardiac diseases	7	5	2
PAD#	9	5	4
Diabetes Mellitus	2	0	2
Stroke	5	2	3
Rheumatic complaints	18	8	10
Cancer	6	3	3

* The information is from the interview in 2001/2002. # BMI=Body Mass Index, COPD= Chronic Obstructive Pulmonary Disease, PAD= Peripheral arterial disease

Results

Fourteen non-frail and eleven frail respondents participated (Table 1), including fourteen men and eleven women; the mean age was 78.7 years (range 67-90). Both the frail and the non-frail suffered from chronic diseases.

Meaning of successful aging according to older persons

For successful aging the following dimensions emerged: staying healthy and maintaining good cognitive functioning, psychosocial functioning, maintaining a good financial situation and staying active. According to the respondents, successful aging was a process of staying in good health, being independent, having a positive outlook, feeling well and being able to perform activities that one likes. Successful aging was described as the process of how persons aged; it was not a judgment about one moment in time. Respondents evaluated their aging process from when they were younger (around the age of 60 years) until the moment of the interview.

Health was considered a prerequisite for successful aging as well as good cognitive functioning. Having social contacts and maintaining these contacts were important criteria. Respondents with a partner reported staying together as a criterion for successful aging. Furthermore, helping other people was a criterion mentioned by the respondents. For some respondents, mostly men, aging successfully meant that they had had success in their work. Some respondents said that because they had had a good job, they were financially able to go on trips and do everything they liked to do. Maintaining a good financial situation was important for successful aging, to be able to afford necessary things and to be able to afford things that give one pleasure. Some respondents mentioned that maintaining a positive attitude, being satisfied with life, was very important to age successfully. People who complained a lot were not considered to be aging successfully. It was considered important for successful aging to put things in perspective and to see that many persons are worse off than oneself.

Education and upbringing were mentioned as important to successful aging because the respondents had learned skills that they used their whole life, such as saving money throughout life, so that in old age they did not have to worry about money. In addition, to age successfully, respondents stated that each person has to take action earlier in life, one needs to think about how one would like to age and

take actions, such as guaranteeing of one's retirement pension, maintaining a healthy lifestyle, avoiding stress, taking care of one's body and arranging finances properly so that in old age a person has enough money.

Man 81 years, not frail.
Successful aging. I feel success is something that happens to you when you are working, when you're trying to go as far as you can in your career.
And that is something that always worked out okay for me, and I am pleased that I can say that I was able to buy my own house and I have a car. I renovated my house myself. I've always been able to earn a few cents and, yes, I feel successful.

Man, 67 years, not frail.
Well, successful aging is a relative term, but if you are able to do what you used to, and you have made sure that you can, well then I feel that you are aging successfully. With successful aging, there are always certain things, I mean I have enough things around me. And I experience things around me. I do things that give me pleasure in aging, creating circumstances that let you do the things you enjoy. So, you can do a lot of things, like traveling. It does not have to be traveling, but you can do things you enjoy. Now that you are older, you finally have the opportunities to do things. I mean older than 60 because I feel that older adults begin to age after that.

Man, 81 years, frail.
I: Can you think of somebody that you feel is aging successfully?
And could you please describe to me why you feel this person is aging successfully.
R: Good health, mentally stable, physically very active.
And, well, a positive outlook, not complaining about everything.

Woman, 81 years old, frail.
Well successful aging means that one is healthy and still enjoys life, that is successful aging to me being healthy and enjoying the activities that one likes and that one has indeed enough finances! I mean to be able to do the things one likes.

Meaning of frailty according to older persons

Three main dimensions of frailty emerged: physical appearance, psychological/ cognitive problems, and social functioning.

The physical appearance dimension included how a person looked and moved around. For example, an old woman who walked with difficulty, with a slow and unsteady gait was considered frail. Furthermore, a pale color of the skin was mentioned as frail. According to most respondents, frailty was characterized by a state of reduced health, suffering from chronic diseases or other forms of deteriorating health. Cancer, stroke, and heart disease were frequently mentioned as contributing to frailty. In addition, being in a wheelchair and using assistive walking devices were often mentioned as criteria for frailty. The respondents also considered older persons who fall often and/or break their bones easily, as frail. Furthermore, respondents mentioned low body weight, poor vision and poor hearing as criteria for frailty. Older persons who were dependent on other persons were described as frail persons.

Frailty also had a more psychological/cognitive dimension according to the respondents. Not feeling well, not being optimistic, not being satisfied with life and feeling down were reported as criteria for frailty. In addition, the respondents often mentioned fear as a criterion for frailty. They mentioned fear of falling, fear of breaking a hip and fear of being robbed. Another criterion frequently mentioned was poor cognitive functioning. In addition, frailty meant not being able to do the things the respondents enjoyed to do.

Furthermore, a dimension of frailty was reduced social functioning. The respondents mentioned feeling lonely and having few social contacts. Not being able to enjoy social contacts or not being able to meet with friends and family was mentioned.

In sum, frailty is viewed as a state that is characterized by reduced health together with psychological and social problems that leads to a situation in which a person is not able to do what he/she enjoys. It was considered a combination of physical problems with psychological problems such as anxiety and feeling down. According to older persons, frailty is thus a multidimensional construct.

Woman, 80 years, not frail.
I (interviewer): When would you say that somebody is frail or . . .?
R (respondent): Well, if you can't see well. That seems horrible to me.
Now I have contact lenses; I had cataracts. Well, frailty, what else is it?
If you cannot walk anymore. You see that every now and then. A lot of old people live in this building and you see their health failing. That seems terrible to me.
I: So if somebody has difficulty walking and . . . ?
R: Yes. That kind of difficulty.

Man, 79 years, not frail.
R: Well, then I would have to tell you about my youngest sister. She is quite frail. She lives in fear. Well, I don't know if she is as fearful as my wife, but she is afraid of dogs, she is afraid of flying, she does not dare go shopping alone, she is, well . . .
I: So you would say that if somebody is living in constant fear, that makes you frail?
R: Yes. That definitely makes you frail because that makes you dependent on whether somebody wants to hold your hand and go with you, go with you when you go shopping, and yes, then you are dependent on other people. I think that makes you frail.

Woman, 69 years, frail.
R: Well look at my sister. Physically her health is declining terribly. She used to be a beautiful women and she can no longer take part in things. She lived at the park and she worked with young people as a volunteer for 30 years. Now she can't do that any more. My other sister and her husband will be 65 years old and there will be a brunch but she cannot go because of her stoma and I think that is so sad.
I: Is that the reason you say your sister is frail?
R: Yes. Yes, definitely, because she always loved doing things for other people so other people would have fun. Now she cannot take part in things anymore that she always loved to do and were fun for her too.

Man, 75 years old, frail.
Well there is a man in this building. He used to be a teacher and nowadays he walks with a walking-cane, he trembles when he walks. The way is health his declining, I find that awful for him. Last time he went away with a bus trip and he was so worn out, the next day he could not do anything. He did not go on the next bus trip and he stayed home. Well his wife was able to go and she went. But I mean I find it pitiful that he was all alone at home that day.

Table 2. Self-categorization as Successful Aging or Frailty.

Choice of respondents	Total sample N=25	Non-frail N=14	Frail N=11
Successful aging	17	12	5
Frailty	5	0	5
Both*	3	2	1

*These respondents could not decide and chose both

Self-categorization as successful aging or frailty

Of the eleven frail respondents, five reported to age successfully, five reported to be frail and one respondent chose both (Table 2). Of the fourteen non-frail respondents, twelve reported to age successfully and two respondents could not decide and chose both. Respondents argued that health was of great influence whether one becomes frail or aged successfully. The concepts were viewed as different from one another in a sense that frailty was described as a state, a situation of health problems combined with other problems. Successful aging was described as the process of how people aged while staying healthy and maintaining cognitive, social functioning and staying active. Both concepts could be present at the same time but this was dependent of the health of the older person. Those who reported to age successfully more often reported better health (Table 3) and mentioned that they were aging successfully and feeling not frail at all. Those in less good health mentioned that the concepts were present at the same time. They stated that they were partly frail because of their health problems (in a frail state) and were partly aging successfully. Being partly frail does not exclude aging in a successful way (the process of aging). Those who were in poor health mentioned that they were frail and not aging successfully because their health restricted them in many ways.

The mean number of chronic diseases was 1.5 (range 0-4) for those who reported to age successfully. The mean number for those who reported to be frail was 2.6 (range 1-5) and 2.3 (range 2-3) for those who chose both. More than half of the non-frail persons reported that frailty/aging successfully is something that can be prevented/increased by taking actions, such as maintaining a healthy lifestyle and exercising. The frail persons more often reported that frailty/successful aging was something that happened to a person, and that a person could not influence much; they felt it all depended on whether ones health remained good. The frail persons

reported also that maintaining a healthy lifestyle could help to age successfully. A few frail respondents thought that only a lucky few age successfully and that most people become frail.

Table 3. Self-categorization and self-perception of Health

Choice of respondents	Number of chronic disease (range)	Self-perception of own health satisfactory
Frail persons		
Successful aging (5)	(0-4)	5
Frailty (5)	(1-5)	1
Both (1)	2	1
Non-frail persons		
Successful aging (12)	(0-3)	11
Both (2)	(2,3)	2

Discussion

This study explored the meaning of frailty and successful aging to older frail and non-frail respondents living in the community, which few studies have done so far. Frailty was considered to consist of three dimensions: physical appearance, psychological/ cognitive problems and social functioning. For successful aging, the dimensions staying healthy & maintaining cognitive functioning, psychosocial functioning, maintaining a good financial situation and being active emerged.

The concepts of frailty and successful aging were viewed as different in such a way that frailty was described as a *state* of health problems combined with other problems and successful aging as the *process* of how people aged. When health decreased, people gradually became frail and found themselves no longer aging successfully. A similar finding was reported by Steverink et al. (30) adults with poor subjective health were more like to frame the aging process in terms of physical decline and social loss instead of continuous growth.

Most definitions of frailty found in the literature include physical frailty markers (16;31). When criteria for frailty that respondents named are compared to the nine of

our own definition of frailty (27), we observe that five criteria: low body weight, poor cognitive functioning, poor vision, poor hearing, feeling down and depressed were mentioned by the respondents in this study. From the five criteria proposed by Fried et al. (20) and that are often used in recent research, two criteria: weight loss and slow walking speed were mentioned by the respondents. This study showed that for older persons frailty, besides health problems, also denotes psychological and social problems.

The definition of successful aging according to Rowe & Kahn exists of three parts: low probability of disease and disease-related disability and absence of risk factors for disease and disability, high cognitive and physical functional capacity, and active engagement with life (1). High cognitive and functional ability and active engagement were mentioned in this study. Low probability of diseases and disease-related disability and absence of risk factors for disease and disability were not mentioned. However, when asked what actions they took to ascertain successful aging, most respondents mentioned maintaining a healthy lifestyle, eating healthy food, exercising, not smoking or abusing alcohol.

The definition of Rowe & Kahn is very strict; in order to age successfully, a person cannot have a chronic disease. In this study, only six respondents had no chronic disease, which implies that these six persons could be classified as aging successfully. Furthermore, eleven respondents were frail, which is a state of moderate or poor physical functioning; these respondents would not meet the Rowe & Kahn criteria for successful aging. Only four non-frail persons without any chronic disease who might be classified as successful aging in this study according to the Rowe & Kahn criteria. This proportion is similar that in the study of Strawbridge et al (15) and the study of Von Faber et al. (11). In contrast, the majority of older persons in our study and in other studies (11;12;15) stated to be aging successfully. Thus, the definition of successful aging could be broadened to better reflect the perceptions of older persons on successful aging. Perhaps the criterion having no chronic diseases could be replaced by a criterion like being able to do what one likes, regardless of chronic diseases. This is in agreement with successful aging as the adaptive *process* of selective optimization (concentrate on activities that one prioritizes) with compensation (for example technological support) (32-35).

The respondents who were in better health and reported to age successfully, more often mentioned the importance of taking actions, such as exercising and

maintaining a healthy lifestyle. The frail respondents more often stated that becoming frail is a process that cannot be controlled. Sarkisian et al. (4) reported that older adults with lower expectations with regard to aging did not believe that it was important to seek health care. Therefore, for health care professionals it is important, when they see older persons, to ask how they think about health and prevention. For frail persons staying physically active, maintaining a healthy lifestyle and preventive actions can possibly postpone further decline in health even when they may be less likely to seek health care.

Similar to the findings of Strawbridge et al. (15) and Knight & Ricciardelli (9), we found that many older persons reported to age successfully, while most suffered from chronic diseases. It appeared that the respondents had clear criteria for successful aging but were less strict to apply these criteria to themselves. The respondents adjusted to their health problems. Likewise, successful aging was shown to be considered as successful adaptation to physical limitations in the study of von Faber et al. (11).

The definition of frailty could be adjusted to better reflect the perspective of older persons to develop a more valid definition of frailty. This adjustment should include ideas of older persons to make the definition more relevant to the older persons. Further research needs to consider psychological and social factors as part of frailty, as it was always a combination according to older persons in our study. Future definitions of successful aging should include physical, psychological, cognitive, and social functioning to better reflect the meaning of older persons. Further research needs to examine why older adults are less strict to apply their criteria of successful aging on themselves as applying their criteria on others.

The concept of successful aging the respondents found easier to define whereas the concept of frailty the respondents found harder to define. This might be a result of the Dutch translation of the word frailty (kwetsbaarheid), which by some respondents was interpreted as vulnerability, in particular in the meaning of easily getting offended in one’s feelings. It was difficult to find a Dutch word for frailty that was easily understood by all respondents. Another limitation of this study, as in all qualitative studies, is the risk of subjectivity. To reduce the risk of subjectivity, two researchers coded the transcripts and the themes were discussed with the other authors.

Furthermore, the results may not be representative of other populations as the sample of respondents was based in Amsterdam and vicinity. The aim of qualitative studies is to explore areas of which little is known about to gain novel understandings about phenomena such as feelings and thought processes. Therefore, a sample that facilitates maximal information is selected (25;26). In this study, to facilitate maximal information on frailty and successful aging, a sample of frail and non-frail persons was selected.

A final limitation is that this study included frail and non-frail persons according to the last measurement cycle of LASA in 2001/2002. To have a great as possible contrast, the group non-frail persons were defined as having none of the frailty markers in 2001/2002. The health of respondents is likely to have deteriorated since that time, so that the participants in the non-frail group most likely had some frailty markers present at the time of the interview.

In conclusion, according to older adults, frailty is a state, characterized by reduced health, psychological and social problems, in which the person is not able to do what he/she enjoys. Successful aging is a process of staying healthy and active, doing things one likes to do.

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Chapter 8

General Discussion

General discussion

In this chapter, the main findings and conclusions of the studies presented in this thesis are summarized and discussed. This thesis focuses on frailty and its consequences, possible risk factors for frailty and the meaning of quality of life, frailty and successful aging to frail and non-frail persons. It contributes to the literature in that the assessment of frailty includes a cross-sectional and longitudinal definition of frailty. Furthermore, the definition of frailty includes physical as well as psychological frailty markers. It also examines several biological risk factors both cross-sectionally and longitudinally. Furthermore, the effect of frailty has been studied independently of the effects of chronic diseases and disability. Moreover, the meaning of quality of life, frailty and successful aging to frail and non-frail older community-dwelling older adults has been examined.

Frailty is a term that is used to indicate a delicate balance with a high risk for negative health outcomes such as falls, disability, institutionalization, and mortality because of multisystem decline in older persons. Frailty is a health problem that increases with aging. The life expectancy will increase in the next thirty-five years. Therefore, it is likely that the number of people suffering from frailty will also increase.

There is no consensus about the definition of frailty. Due to the variety in definitions, the estimates of older persons suffering from frailty vary from 6 percent to 40 percent. In this thesis, frailty is defined as present when a subject has scores above the cutoff on three or more out of nine frailty markers. These frailty markers are body weight, peak expiratory flow, cognition, vision and hearing capacity, incontinence, sense of mastery, depressive symptoms and physical activity. Frailty is defined in a static and dynamic way. The static definition includes low functioning at one moment (one measurement cycle of LASA) and the dynamic definition is based on the change in the frailty markers between two moments (two measurement cycles from LASA).

This chapter describes the main findings and some of the methodological issues that have arisen from the studies presented in this thesis. The chapter concludes with the relevance and implications for public health and clinical practice, and recommendations for future research.

Main findings

The relationship between frailty and adverse outcomes

The negative effects of frailty were reported in chapters 2,3 and 4. An overview of the adverse outcomes and the dynamic and static definition is presented in Table 1. Static frailty was associated with physical decline measured with performance tests only in persons in the middle tertile of age (71-78 years) in the subsequent three years. In all older persons, it was associated with decline measured with self-reports on functional limitations. Dynamic frailty was associated with performance-based decline only in women, but with self-reported increase in functional limitations in both men and women. These effects were independent of the effect of chronic diseases. Frailty according to the static definition increased the risk of physical decline to a greater extent than frailty according to the dynamic definition (chapter 2).

Frailty was associated with an increased risk of institutionalization in both men and women using both definitions of frailty (Table 1). More women than men were admitted to a residential/ nursing home in a period of six-year follow-up. Frail persons had a twice-higher risk for institutionalization than non-frail persons. Static frailty increased the risk of institutionalization to a greater extent than dynamic frailty (chapter 3).

In addition, the relationship between frailty and mortality was also studied. Between the first follow-up of LASA (1995/1996) and January 1, 2000, 328 persons died (209 men and 119 women). Frailty according to the static definition increased the risk of mortality for both men and women (Table 1). Frailty according to the dynamic definition increased the risk of mortality in women only (chapter 4).

All single frailty markers were associated with at least one adverse outcome measure in a static or dynamic way (Table 2). In addition, the frailty markers weight loss, decline in physical activity, cognitive impairments/cognitive decline and depression/increase in depressive symptoms were often associated with the adverse outcomes. This is in contrast to other single frailty markers, which often were not associated with the adverse outcomes of frailty, i.e. loss of hearing and incontinence. However, when all single markers were combined into a summed frailty index, the risk for adverse outcomes increased with the number of frailty markers (Table 1). This index represents multisystem decline.

Table 1. Association between frailty and adverse outcomes adjusted for confounders

Frailty definition	Physical decline		Institutionaliza-tion**	Mortality***
	Performance test*	Self-reported decline*		
Static frailty†	+ Only for 71-78 years	+	+	+
+Chronic diseases	+ Only for 71-78 years	+	+	+
+Disability	#	#	+	+
+Chronic diseases and disability	#	#	+	+
+Chronic diseases and dynamic frailty	+ Only for 71-78 years	+	#	#
+Chronic diseases, disability and dynamic frailty	#	#	+	+
Increasing number of frailty markers	+	+	+	+
Dynamic frailty†	+ Only women	+	+	+ Only women
+Chronic diseases	+ Only women	+	+	+ Only women
+Disability	#	#	+	+ Only women
+Chronic diseases and disability	#	#	+	+ Only women
+Chronic diseases and static frailty	+ Only women	No significant association	#	#
+Chronic diseases, disability and static frailty	#	#	No significant association	+ Only women
Increasing number of frailty markers	+ Only women	+	+	+ Only women

†All models include frailty and additional variables were added
*Adjusted for age, sex and education
**Adjusted for age, sex, care received, partner status and income.
***Adjusted for age and education.
+ Frailty increased the risk of the adverse outcome for all subjects unless otherwise specified.
# Not examined.

Table 2. Associations between single frailty markers and adverse outcomes

Static Frailty markers	Physical decline		Institutionali-zation	Mortality
	Performance test	Self-reported decline		
Low BMI				+
Low peak expiratory flow		+ Only women		+
Cognitive impairments		+	+	+
Poor vision		+		+ Only women
Poor hearing	+			
Incontinence		+	+	
Low mastery		+	+	
Depression		+	+ Only men	+
Low physical activity	+	+	+	+
Dynamic frailty markers				
Weight loss	+	+ Only men	+	+
Decline of peak expiratory flow		+	+	+ Only women
Decline in cognitive functioning		+	+	+ Only women
Loss of vision	+	+		+ Only women
Loss of hearing				
New incontinence				
Decline in mastery		+		
Increase in depressive symptoms		+	+	+
Decline in physical activity		+	+	+

Biological risk factors and frailty

In this thesis, the effects of four biological risk factors were examined. The outcome was prevalent frailty in 1995/1996 and incident frailty in a three-year period (1998/1999). Compared to high serum 25(OH)D, low serum 25(OH)D and moderately low serum 25(OH)D were associated with prevalent frailty. The respondents with lower serum 25(OH)D levels were more often frail. None of the other serum markers was associated with prevalent frailty. Moderately elevated CRP levels predicted incident frailty, as did low serum levels of 25(OH)D. Similar results were found with multinomial logistic regression analysis using the number of frailty

markers as the outcome. No consistent associations were observed for IL-6 and IGF-1 (chapter 5). The finding that moderately elevated levels of CRP were associated with incident frailty is in agreement with the hypothesis that chronic low-grade infection contributes to frailty.

Frailty, quality of life and successful aging.

The outcome quality of life was studied in this thesis from the perspectives from the older persons (chapter 6). Quality of life is seldom defined and the meaning of the concept of quality of life for older adults has not been thoroughly investigated. Furthermore, it was examined if important aspects for quality of life differed between frail and non-frail community-dwelling older adults. Good quality of life meant good physical health, psychological well-being, having social contacts, performing activities to enjoy, activities to help others, activities to maintain or improve physical health, activities to meet other people and having a nice home and living in a safe neighborhood. The aspects did not differ between frail and non-frail respondents. Most respondents (22 of 25) found that their quality of life was satisfactory to good. However, those who were frail rated their quality of life on average lower than non-frail persons.

Frailty according to older persons was a state characterized by reduced health, psychological problems such as being anxious and feeling down (chapter 7). Furthermore, frailty meant few social contacts and feelings of loneliness. Somebody was considered frail when not able to do things that he or she enjoyed. When the definitions of frailty described by the older persons were compared to existing definitions of frailty, it was observed that the latter mostly include physical components, but the concept according to older persons also comprised psychological and social aspects.

Successful aging was described as a process of growing older, in good health (physically and mentally), having a positive outlook, being active, and having social contacts (Chapter 7). It meant being able to do the things one likes to do. The majority of the respondents (17 of 25) reported that they were aging successfully.

Considerations as regards content

Frailty increased the risk of adverse outcomes. Although frailty is conceived as a dynamic state with high risk of adverse outcomes, most investigators studied frailty at a single moment, in a static way. In these models, the adverse outcomes are predicted by baseline characteristics in which no deterioration in health is included. However, change in health reflects the definition of frailty indicating an unstable state with high risk for adverse outcomes. Dynamic frailty indicates decline from a certain level of functioning to a lower level of functioning. It is possible that a person is frail in a dynamic sense but not in a static sense. This means that this person declines from a high level of functioning to a lower level of functioning in three or more areas, but not always to the lowest level (static frailty). This person might experience a loss of precarious balance. The dynamic definition of frailty, however, was not as predictive for the outcomes studies as the static definition as it often lost significance when adjusting for the definition of static frailty. Frailty according to the static definition more often increased the risk to a greater extent than frailty according to the dynamic definition.

A tentative explanation is that persons who decline from a high level of functioning to a lower level still might have the ability to cope with stress, whereas persons at a low level of functioning have passed the threshold of frailty and are at high risk for adverse outcomes.

Frailty was more often present in women and increased the risk of adverse outcomes more often in women than in men. Women may be more susceptible for frailty, women had more frailty markers present than men. These findings are supported by other studies, which also found a greater prevalence of frailty in women (1-3). Predictive ability of some frailty markers was only observed in women (Table 2), especially for the outcome mortality. Women in the Netherlands spend on average almost twenty years of their lives in suboptimal health whereas for men this is only 14 years (4). Women are more likely to become frail in this period of 20 years. A recent study investigating four patterns of functional decline in the last phase of life, found that frail subjects were most likely to be women and were relatively more disabled through the last year of life whereas men died more suddenly and more often from cancer (5). The three-year measurement cycles of LASA might have been too long to measure frailty in men.

In addition, women were more often admitted to residential/ nursing homes than men. The reasons for admission are not available in our study but would be very interesting to know: were the respondents admitted because of frailty or were they admitted because of lack of informal care in the home? The women more often lived alone; men more often lived with a partner. The partner can help in preventing or postponing frailty, can promote physical activity by exercising together, can warn a health care professional in case of declining health or depressive symptoms, and prepare meals which may postpone frailty markers such as weight loss. Moreover, having no partner in the household was associated with increased risk of admission in the model investigating the effect of static frailty. Men had less often functional limitations and less severe limitations than women. These functional limitations increased the risk for admission only in men in contrast to women. Availability of the reasons for admission could give more insight into the differences between men and women in terms of factors leading to admission.

Walston & Fried (6) have described several physiological mechanisms as possible explanations for sex differences in frailty: men have more muscle mass and higher levels of neuroendocrine and hormonal factors that may protect them from reaching frailty. Women more often suffer from chronic inflammatory diseases, a mechanism that is hypothesized to cause frailty. However, when investigating biological risk factors, we found no sex differences in the relationship between the biological risk factors and incident and prevalent frailty. It is possible that other biological risk factors such as anemia, and other endocrine and inflammatory markers than those studied or interactions between these factors. They may have a different impact on incident and prevalent frailty for men and women.

Methodological considerations

In this paragraph several methodological considerations are described concerning the studies in this thesis in more general terms, a discussion that is presented in more detail in each chapter.

Longitudinal Aging Study Amsterdam (LASA)

In four of the studies described in this thesis, data from previous cycles of the Longitudinal Aging Study Amsterdam (LASA) were used. A major strength of LASA is that it collects information on all areas of functioning, which makes it possible to

investigate consequences of a variety of aspects for other areas of functioning. The LASA design makes it possible to study the pathways of frailty prospectively, which gives more insight into the pathogenesis of frailty than cross-sectional studies.

A limitation of cohort studies like LASA is the loss to follow-up. Attrition is a threat to all longitudinal studies and this may have affected the generalization of the results. LASA was stratified at the start in 1992/1993 by age, sex and five-year expected mortality to improve external validity. External validity can be best described as the validity of the results when extrapolated to other populations than the sample studied. Nevertheless, respondents lost to follow-up had more often chronic diseases, were older, more often cognitively impaired, suffered more often from depression and more often lived alone. The remaining sample may be a relatively healthy part of the original sample. This became a problem when investigating the risk of frailty for decline in performance tests and self-reported decline. To complete all performance tests, respondents had to understand the test and be physically able to perform the test whereas self-reports were easier to complete physically. Results showed that respondents who declined in performance were in better health than those who declined in self-reports, showing more loss to follow-up of the more frail respondents in the sample to study performance-based decline. This possible selective dropout of the more frail persons could have led to underestimation of our results. Persons who have less favorable health have most likely an increased risk of adverse outcomes as opposed to more healthy individuals. However, in studies examining the effect of attrition on the outcomes, attrition only had effect on the description of the sample but not on the outcomes (7-10), so the effect of attrition on the risk of adverse outcomes is not clear.

Frailty definition and frailty markers

A limitation of our study is that all independent variables were dichotomized; suggesting that information about the subjects may have been lost. To establish an operational definition of frailty, cutoff points had to be chosen. The choice was based on earlier studies (1;11-18). Another limitation is related to the determination of change in the dynamic frailty markers. For several frailty markers (cognition, peak expiratory flow, physical activity, depressive symptoms and sense of mastery), no definition of relevant decline was found in the literature and therefore a definition of relevant decline had to be made. For weight loss, incontinence, decline in vision and

hearing capacity, a definition of decline was available. For the variables cognition, as measured with the Mini Mental State Examination (19), sense of mastery, as measured with the short version of the Pearlin and Schooler mastery scale (20), and physical activity, as measured with the LAPAQ (21), relevant decline was determined using the Edwards-Nunnally Index to calculate decline for each of these frailty markers (22). The Edwards-Nunnally index can be used to calculate individual significant change, which is a strength of this index. The individual significant change is calculated taking into account the reliability of the measurement instrument, the confidence interval and the population mean. This index has been developed to determine pre-test-post-test recovery. It classifies pre-post-test change as improved, no change, or deterioration using the confidence interval. If the post-test score lies outside the confidence interval, it is considered significantly different from the pre-test score. Another strength of this index is that the pre-post-test change is adjusted for regression to the mean. However, it is not possible to determine just from the pre-test and the post-test score whether an individual has significantly changed. To determine this, one needs additional information about the reliability of this measurement instrument and the population mean. A health care professional cannot use this index to determine decline for a patient he/she is treating. The Edwards-Nunnally index, therefore, is a good instrument to determine change in epidemiological studies but not in clinical practice.

A further limitation is that we did not study the effect of combinations of frailty markers. It is possible that certain combinations increase the risk of adverse outcomes more than other combinations. We tried to study the effect of combinations of three or more frailty markers but there are 84 possible combinations of the nine frailty markers. The most frequent combination of static frailty markers for all outcomes consisted of incontinence, a low sense of mastery and depression. The most frequent combination of dynamic frailty markers for the outcomes decline in self-reported functioning and institutionalization was declines in peak expiratory flow, cognitive functioning and physical activity. For the outcomes decline in performance test and mortality, the most frequent combination was decline in sense of mastery, increase in depressive symptoms, and decline in physical activity. Most of specific these combinations of three frailty markers had a low prevalence. This made statistical analysis difficult to perform, since sufficient number of persons with the combination of three specific frailty markers must experience the adverse outcome

studied, like mortality or physical decline. However, for these combinations of physical and psychological problems as mentioned above, it is imaginable that these combinations would lead to adverse outcomes.

A further limitation is related to the determination of dynamic frailty itself. Dynamic frailty was defined as change in three or more frailty markers between two measurement cycles. Since frailty is defined as a precarious balance resulting from impaired physiological reserve, three years is a relatively long time to determine change. Recent studies have shown that transitions between disability states occurred very often in frail respondents even when using three months time intervals to measure transitions (23;24). Frailty is most likely to be a process that will occur in a shorter time interval than three years. It is possible that the frailest persons developed frailty more quickly and these persons were lost to follow-up before the next measurement cycle, leaving only respondents who recently declined in functioning or who slowly declined over a period of three years. Moreover, decline determined at a three-year interval is not useful for clinical practice. A health care professional cannot wait three years before determining if his or her patient is frail. However, this is the first study that used a dynamic definition of frailty and it was shown to be predictive for adverse outcomes of frailty.

Biological risk factors

The four biological risk factors studied in this thesis were serum concentrations of 25-hydroxyvitamin D (25(OH)D), interleukin-6 (IL-6), C-reactive protein (CRP), and insulin-like growth factor-1 (IGF-1). A limitation is the high detection limit of IL-6 of the method used in our study, which resulted in few respondents with valid IL-6 values. This has limited the power of the analyses, for both the study of this single risk factor and the study of possible interaction between the four risk factors. The interaction between IL-6 and IGF-1 observed in other studies (25;26) was not confirmed in our study, possibly due to the small number of people with the combination of high IL-6 and low IGF-1 values. Furthermore, a limitation is the determination of these risk factors at one point in time. Cytokines are quickly released in response to different stimuli; pathogens, physical trauma and chemicals stimulate monocytes, macrophages and other cells to produce cytokines that induce the inflammation process (27-29). Circulating cytokines have a short half-life time. Increased IL-6 leads to fever, activation of the hepatic acute phase response and decline of

hemoglobin levels (27;30). The assessment of the biological risk factors only at one moment may have resulted in measurement of acute infections, rather than the chronic inflammatory state that is hypothesized to cause frailty.

Outcome measures

In this thesis, we used the outcome measures physical decline (measured with the performance tests and self-reported functional limitations), institutionalization, mortality, and prevalent & incident frailty. Decline in physical functioning was measured over a period of three years. Frailty was more strongly associated with decline measured with self-reports than with the performance tests. Both self-reports and performance tests are valid and reliable measures but measure different aspects of physical functioning and therefore can be considered to complement each other (31-34). In two other LASA-studies by Stel et al. (35) and Schalk et al. (36), differences were found with respect to self-reports and performance tests. Stel et al. (35) found that self-reports were more strongly associated with fractures than performance tests, Schalk et al. (36) found that low serum albumin was only associated with substantial decline in self-report and not in performance-tests. Those who completed the performance tests were likely a healthier group than those who completed self-reports. Frailty may have had less impact on the more healthy subjects. On the other hand, information bias (distortion of the results of the study as a consequence of errors in measuring one or more variables in the study), could have led to misclassification with regard to self-report. Especially the older, cognitively impaired persons may have answered the self-reported functional limitations too positive or too negative. For the outcome decline in physical functioning, the tests scores were dichotomized into decline versus no decline for easy interpretation of the effects of frailty on adverse outcomes. A few respondents improved in physical functioning. Improvement was not examined in this thesis but it would be interesting to know determinants of improvements in functioning.

The incidence of admission to a residential-/nursing home was calculated between the first follow-up (1995/1996) and the third follow-up (2001/2002). For almost all respondents, the residential status was known. For the very few respondents for whom the residential status was unknown, sensitivity analyses were carried out; no differences in the results were found. A limitation however is the lack of exact date of institutionalization and reasons for admission to a residential-/nursing

home. In the analysis, the date of admission was assumed at midpoint between the interviews. This might have resulted in less precise estimates.

The increased risk of frail elderly for mortality was also examined in this thesis. Vital status ascertainment was 100 percent complete. Frailty increased the risk for mortality. However, this effect was greater for women than in men. Perhaps other frailty markers increase the risk of mortality in men than those included in this study.

The effect of four biological risk factors on prevalent and incident frailty was examined. It is very likely that other factors, besides the biological risk factors included in this study, have contributed to the development of new frailty. Three years is a long period in which many health events in older persons can take place so it remains difficult to investigate the relationship of inflammation and frailty. However, this is one of the first studies that examined the effects of biological markers and frailty longitudinally.

Confounders

The concepts of frailty, disability and chronic diseases have been frequently used interchangeably (37). Whether frailty has a unique effect on adverse outcomes has not been frequently investigated. Therefore, in this thesis analyses were additionally adjusted to study if frailty had an effect independently of chronic diseases and disability on adverse outcomes.

The total number of chronic diseases was frequently included to examine whether the effect of frailty was independent of that of chronic diseases. In the LASA study seven chronic diseases are included: chronic obstructive pulmonary diseases, cardiac disease (myocardial infarction, arrhythmia's, congestive heart failure, angina pectoris and narrowing of the coronary arteries), peripheral arterial disease, diabetes mellitus, cerebrovascular accidents, rheumatoid arthritis or osteoarthritis (both conditions were grouped together because respondents appeared to find it hard to differentiate between them) and cancer. The presence of the chronic diseases was self-reported and this might have resulted in information bias (over- or underreporting of diseases by the respondent). Agreement between respondents' self-reported data and data from the general practitioner has been shown to be satisfactory to good for most diseases studied (38).

A limitation however is that we have no data from the general practitioner about the severity of the disease. Some chronic diseases have a greater impact on

functioning than other chronic diseases. The severity of a chronic disease will, together with frailty, determine the consequences for functioning. Furthermore, other diseases, which might have a great effect on functioning, such as Parkinson's disease, were not included in this study.

Another confounder investigated for the outcome institutionalization, was the care received. The respondents were asked if they received help with household activities or personal care and from which person they received help. The help was divided into the categories informal care, professional care paid out of the pocket, and professional subsidized care. Most respondents received no help or informal care, which is probably mostly help with housekeeping. A small number of respondents received help from professionals, and even fewer received help with personal care from professionals. This did not make it not possible to take the hours of professional help received into account. Therefore, the analyses are limited by the rather crude way of measuring the care received.

Analyses

All studies were carried out using logistic regression analysis or Cox proportional hazard analysis. In the study of investigating the association between biological risk factors and frailty, logistic regression analyses were used. Separate analyses were carried out to investigate the cross-sectional associations and longitudinal associations. However, the sample for the longitudinal association is smaller because of loss to follow-up. Another technique to investigate these associations is Generalized Estimated Equations (GEE). This technique takes missing data into account and is suitable to investigate cross-sectional and longitudinal associations in one analysis. It is a sophisticated way to analyze longitudinal data from studies such as LASA. We performed GEE to study the effect of the biological risk factors. Low serum 25(OH)D and CRP were associated with frailty. However, because cross-sectional and longitudinal effects cannot be separated, its use for clinical practice is limited. In this study, separate logistic regression analyses gave more insight in both kinds of associations between the biological risk factors and frailty. Nevertheless, results from the GEE were similar to the results of the logistic regression analyses.

Qualitative study, strengths and limitations

A major strength of qualitative design is that feelings, meanings and motivations can be explored more in depth, without the limitations of a questionnaire in which the person can only chose between pre-defined answer categories. As quality of life is expected to mean different things for different people, a qualitative design is more appropriate to explore the meaning of quality of life. Furthermore, the meaning of frailty and successful aging to older adults were explored. A limitation of this study as in all qualitative studies is the risk of subjectivity and the generalization of results. To reduce the risk of subjectivity, two researchers coded independently. The sample cannot be considered representative of the population of older community-dwelling adults. It was a small select sample of respondents in Amsterdam and vicinity. Therefore, results cannot be generalized to other populations.

Frailty was a term that respondents found harder to define and was sometimes defined in a way of sensitive for being offended. This might be a result of the Dutch translation of the word frailty (kwetsbaarheid, broos, fragiel). It was difficult to find a Dutch word for frailty that was easily understood by all respondents. Because of the difficulty in measuring frailty, length of the interview (mean duration was 1.5 hour), the connections between the three concepts quality of life, successful aging and frailty, were only explored in few respondents, making it difficult to draw conclusions on these connections.

Relevance and implications for public health and clinical practice

Frailty is an increasing health problem of the aging population and will likely lead to an increasing use of health care services (39). An increasing number of people will grow old and their life expectancy will increase in the next thirty-five years. Therefore, it is likely that the number of people suffering from frailty will also increase. Older people who are frail are at risk of becoming dependent and will use more often health care services such as home care, residential and nursing home care, with subsequently rising costs. With the growth of the older population there has been increasing concern about its well-being, both from the perspective of the individual and that of society, which is faced with the challenges of meeting their health and social care needs (39;40). When we compared frailty-free life expectancy to disability-free life expectancy (mild disability as well as severe disability), it was shown that the population impact of frailty was greater than the impact of severe

disability (41). Frailty can lead to use of health care services can have a considerable impact on quality of life for older persons. Interventions to prevent or postpone this are necessary.

Defining frailty more accurately may enable geriatricians and general practitioners to identify those elderly who will benefit from geriatric assessment and this may result in improved screening of older adults at risk of becoming dependent. This may lead to a more efficient use of health care services. Effective programs for the care of frail individuals can minimize the impact on the individual, their families, and society. Frailty may be a potentially reversible state and may be prevented or postponed (42). Nevertheless, the Interventions on Frailty Working Group stated that preventive approaches for disability have rarely been studied (43). Recent reviews and meta-analyses on assessment of older people show conflicting results. Elkan et al. (44) found that home visits reduced the risk of mortality and institutionalization, but no evidence was found for improvement of health. Stuck et al. (45) found that interventions such as home visits and comprehensive geriatric assessment have been shown to be effective when administered to older people in the beginning stages of frailty, including multidimensional assessment and multiple follow-up visits. Those with more advanced frailty benefited less from the interventions. However, a recent large randomized controlled trial showed little difference for most outcomes when assessment was done in general practice (46). In this trial, a high frequency of unreported and unmet care needs was found. In addition, some recent trials showed benefits for older people by case management (47-49) and an educational program (50).

Thus, although the evidence of the benefits of assessment of older persons is not consistent yet, it is clear that interventions may have potential benefits for health and functioning of older adults when they include an assessment of multiple domains of functioning, with follow-up assessments (51). Continuing functional decline is not inevitable in older people (23;24). If the process of frailty is described more accurately and additional insight into causes and the pathways of frailty is achieved, this could lead to the development of a screening instrument to identify frail elderly. Interventions can be developed, tested and implemented, and frailty may be postponed, thereby increasing the quality of life of elderly people and decreasing their need of care.

A very interesting finding why more research to enhance knowledge about early detection and preventive interventions is important, was reported by Ostir et al. (52). They showed that high positive affect (measured with the positive items of the CES-D) was associated with a significantly lower risk of incident frailty. The opposite of positive affect, depression was associated with all adverse outcomes in this thesis. Treatment of depression and interventions for prevention of depression in older persons are available (53-55). In addition, for other frailty markers interventions are available as well. For example, a study of the effectiveness of a bibliotherapy (increasing self-management ability) had a positive effect on well-being (56). This can increase sense of mastery and prevent symptoms of depression. Exercise and rehabilitation have the potential to improve functional status (57). Maintaining a healthy lifestyle reduces the risk of health decline and mortality (58). Maintaining a healthier lifestyle could possibly postpone the development of frailty markers such as physical inactivity, low peak expiratory flow, weight loss and depression.

Thus, it appears to be important to assess the multiple domains of functioning of older persons to find unmet health needs and have multiple follow-up visits. This comprehensive geriatric assessment can take place in geriatric assessment teams. Older persons wish to live independently as long as possible and wish if they need care to receive that in their home. The multidisciplinary geriatric assessment team can include geriatricians as well as the general practitioner as home care nurses. The general practitioner and home care nurse have more contact with older persons and are therefore more able to monitor the older persons at risk for adverse outcomes. This makes it possible to start interventions by a member of the geriatric assessment team when necessary.

As care is provided to maintain or improve quality of life, the important items to quality of life should be discussed with older persons as these vary between older adults because of different expectations and experiences. In our qualitative study, most respondents were afraid of dementia and admission to a nursing home. The negative ideas about life in a nursing home were from direct experience with a nursing home but also from the media. Lately there has been a lot of negative publicity about the living situation in nursing homes in the Netherlands. Health care professionals should reserve time to discuss the situation and expectations of older adults. Things that were reported to improve quality of life were sometimes very simple, such as medications for pain or adjustments in the house such as a raised

toilet seat or alarm system, or getting help in the household. Older adults found trivial everyday things very important for quality of life whereas a lack of these things can decrease quality of life. Furthermore, feeling unsafe in the neighborhood after dark, or obstacles on the sidewalks, were reported to decrease quality of life.

Surprisingly, those in better health and reporting to age successfully, more often mentioned the importance of taking actions, such as exercising and maintaining a healthy lifestyle. The frail persons more often reported that frailty is something that happens to you, a process that cannot be controlled. Sarkisian et al (59) reported that older adults with lower expectations with regard to aging did not believe that it was important to seek health care. For health care professionals it is important to ask how older persons think about health and prevention. For the more frail persons, staying physically active and maintaining a healthy lifestyle can possibly postpone further decline in health while they may be less likely to seek health care.

Recommendations for future research

Although frailty is a common diagnosis in the elderly population, definitions that have been proposed in the literature thus far are generally based on authors' opinions or questioning experts, and have been the subject of debate and criticism (15). The absence of a widely accepted definition has resulted in inconsistency in the reported prevalence, risk factors and outcomes of frailty and a poor understanding of the potential for prevention and management. So far, most studies investigating frailty have considered primarily a biomedical perspective, neglecting psychosocial variables that are very important aspects for quality of life in older adults. An important part of most definitions of frailty is the high risk of adverse outcomes due to a delicate balance. It is well know that psychological and social resources will influence how people cope with their physical problems. Frailty consisted of health problems, psychological problems, cognitive problems, social problems according to older frail and non-frail persons. Further research is needed to develop a sound definition of frailty, also considering social and psychological factors. In this study, we have used the measurement instruments available in the LASA study. So the definition of frailty used in this study should be validated in another study.

Secondly, the general practitioner or geriatrician requires a simple instrument to determine whether the older person in his/her practice is frail or not and what tailored interventions to start if needed. Recently, attempts has been made to

develop a short instrument to measure change in frailty in clinical practice (60;61). Furthermore, another instrument, the Groningen Frailty Indictor, was constructed to select patients for interventions and was short and easy-to-use (62). These instruments should be validated.

Another recommendation for further research to study the pathways of frailty is to design studies with short time intervals between the measurement cycles. Shorter time intervals will give more insight into the causes, biological risk factors and pathways of frailty.

The mechanism explaining the relation between a low serum concentration of 25(OH)D and frailty is not clear yet. Low 25(OH)D levels have been shown to be associated with low muscle strength, falls and disability (63;64). In observational prospective cohort studies such as LASA, definite causal relationships cannot be established. It is known that a low serum 25(OH)D concentration can be easily corrected by sunlight exposure or vitamin D supplementation of 400-800 IU/day. Supplementation has been shown to improve vitamin D status, bone mineral density and muscle strength in older persons (63-65). However, the impact on frailty has not been investigated. So clinical trials studying the effects of vitamin D supplementation should also focus on frailty as an outcome measure.

Recent studies showed benefits of physical activity with regard to inflammatory markers, as physical activity was associated with lower levels of inflammation (66-71). Physical inactivity is also an important contributor to the development of frailty and loss of muscle mass. Randomized controlled prospective trials are necessary to investigate the effect of physical activity on inflammation. Frailty is conceived to be a dynamic process and therefore multiple assessments of frailty and biological serum markers using short time intervals might show more precisely the effect of biological serum markers on the development of frailty (72). Some risk factors which have not been included in this thesis, show interesting results, such as anemia (73-75) or plasma hypertonicity (76). These biological risk factors might be eventually used for screening older persons to find those at high risk for adverse outcomes (77).

Furthermore, obesity is associated with higher levels of inflammatory markers (78). Of interest is our finding that those who were frail at baseline were more often obese than the non-frail. Moreover, those who became frail were more often obese at baseline than to those who did not become frail. These results suggest that not only low body weight but also obesity should be included as a frailty indicator. Obesity

increases the risk of arteriosclerosis and cardiovascular disease, which both have been suggested as possible pathways leading to frailty (79). A recent cross-sectional study in women, showed that obesity was associated with the frailty concept developed by Fried et al. (80). The possible u-shaped relation between body mass index and frailty should be examined in future longitudinal studies.

Trivial everyday things proved very important for quality of life. Quality of life instruments for older persons should take into account more aspects of social and living conditions. In addition, themes like the fear of dementia and the feelings of unsafeness should be taken into account since these themes proved to be important for quality of life for older adults. Furthermore, researchers developing and using quality of life instruments should try to include expectations about quality of life. Successful aging was shown to be successful adaptation to physical limitations in the study of von Faber et al. (81). The definition of Rowe & Kahn is very strict; in order to age successfully, a person cannot have a chronic disease. The definition of successful aging should be less strictly to better reflect the perceptions of older persons. Perhaps the criterion having no chronic disease should be replaced by a criterion as being able to do what a persons enjoys, independently of chronic diseases. Future definitions of successful aging should include physical, psychological, cognitive and social functioning. In future studies, the connections between the three concepts quality of life, frailty and successful aging, should be further explored as these can show how older persons experience these concepts. It can provide additional information on how to improve quality of life, and prevent frailty with the perspective of successful aging.

Conclusion

The main findings of this thesis include the increased risk of frailty for adverse outcomes and the association between frailty and biological risk factors. Older frail persons have an increased risk for physical decline, institutionalization, and death. Furthermore, a low serum level of 25-hydroxyvitamin D (25(OH)D) was strongly associated with prevalent and incident frailty. In addition, moderately increased serum CRP was also associated with incident frailty. In this thesis we examined a static and dynamic definition of frailty and both definitions increased the risk for negative health outcomes. Static frailty meant that a low level of functioning was related to adverse outcomes, which is not a new finding. Dynamic frailty i.e. change in three or more areas of functioning, not always to the lowest level, also increased the risk for adverse outcomes. Differences were found in the prevalence of frailty between men and women. Women more often were frail and suffered from the negative health consequences of frailty. Frail persons rated their quality of life on average lower than non-frail older persons. Despite of their frailty, most older person still rated their quality of life as satisfactory. Frailty was considered as a state characterized by reduced health together with psychological and social problems leading to a situation when a person is not able to do what he or she enjoys. Successful aging was considered as a process of staying healthy and maintaining good cognitive functioning. Furthermore, it includes having social contacts and doing things one likes to do.

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Summary

Summary

Frailty is an increasing health problem in the elderly. The number of older adults is increasing in the Netherlands and the older persons become slightly older. This leads to an increasing number of frail older persons in the future. Frailty is a term that has not been often used before the past fifteen years. At this moment, multiple definitions of frailty are available, but there is lack of evidence about the causes and pathways leading to frailty. There is no consensus about the definition of frailty and therefore the estimates of the number of older persons suffering from frailty vary from 6 percent to 40 percent. Although there is no consensus yet about the definition, the concept of frailty includes a state of reduced physiologic reserve combined with increased risk of adverse outcomes. Most studies so far used a physical definition of frailty, neglecting the more psychological factors. Frailty is considered a consequence of changes in the neuroendocrine and immune system and musculoskeletal functioning. However, there is little empirical evidence yet.

Although frailty is conceived to be a dynamic state with high risk of adverse outcomes, most investigators studied a single moment definition of frailty, a static definition.

In this thesis, frailty is defined as present when a subject has three or more out of nine frailty markers. These frailty markers are low body weight, low peak expiratory flow, impaired cognition, vision and hearing impairments, incontinence, low sense of mastery, depressive symptoms and low physical activity. Frailty is defined in a static and dynamic way. The static definition includes low functioning at one moment and the dynamic definition is based on the change in the frailty markers between two moments.

The research questions of this thesis are:

1) What is the relationship between frailty and adverse health outcomes of frailty; physical decline, institutionalization and mortality?
2) What is the association between endocrine and inflammatory markers and prevalent and incident frailty?
3) What is the meaning of quality of life to older frail and non-frail adults and are these important aspects of quality of life different for frail and non-frail older adults?
4) What is the meaning of frailty and successful aging to older frail and non-frail persons?

The studies of this thesis were performed within the Longitudinal Aging Study Amsterdam (LASA), an ongoing multidisciplinary cohort study on predictors and consequences of changes in physical, cognitive, emotional and social functioning of the elderly. LASA started in 1992/1993 with 3107 respondents aged 55-85, stratified by age and sex according to expected mortality after 5 years. Every three-year data were collected in a main and medical interview by trained interviewers. In this thesis data have been used from the baseline examination (1992/1993), the first follow-up (1995,1996), the second follow-up (1998/1999) and third follow-up (2001/2002). Blood samples were collected in 1995/1996 in all respondents aged 65 and over. Additional information on the meaning of quality of life, frailty and successful aging in frail and non-frail respondents was collected in a qualitative study using semi-structured interviews with 25 community-dwelling older adults.

In chapter 2, the relationship between frailty and physical decline is described. Frailty was defined in a static and dynamic way. Decline in physical functioning is one of the first adverse outcomes of frailty. Performance-based measures of functional status are modestly associated with self-reported measures on a cross-sectional and longitudinal basis. Therefore, the relationship with both types of measurement instruments was examined. The second question was whether this relationship was independent of the effect of chronic diseases. Physical decline was defined as decline between 1995/1996 and 1998/1999 for both the performance tests and the self-reports. Twenty-three percent declined in performance and twenty-five percent declined in self-reported functioning. Of those who declined in performance, 23% met

the criteria for static frailty, 26% for dynamic frailty and 23 % met the criteria for both definitions of frailty. Of those who declined in self-reported functioning, 34% fulfilled the criteria for static frailty, 31% for dynamic frailty, and 18 percent met criteria for both definitions. Static frailty was associated with decline in performance only in the middle-old group (71-78 years) and with decline in self-reported functioning for all men and women. Dynamic frailty was associated with decline in performance only in women and with self-reported functional limitations both in men and women and these associations were independent of chronic diseases.

In chapter 3, the risk of frailty for institutionalization was studied. Frailty is considered to increase the risk for institutionalization but so far, there is little longitudinal information on the risk for institutionalization for frail community-dwelling older people. Most studies so far have investigated the risk for institutionalization in high-risk groups such as patients with impaired cognitive functioning or a specific chronic disease such as Parkinson's disease. Furthermore, in each country, the care system is organized differently and therefore the results of studies investigating institutionalization cannot be easily compared across countries. In this study, 104 women and 49 men were admitted to a residential or nursing home during the six-year follow-up. Of the persons admitted, 38 percent met the criteria for static frailty, 34 percent met the criteria for dynamic frailty and 20 percent fulfilled criteria for both definitions of frailty. Those who were admitted were older and lived more often alone, had more chronic diseases and more functional limitations. Both static and dynamic frailty was associated with institutionalization in both men and women. Both these associations were independent of the effect of chronic diseases and functional limitations.

In chapter 4, the risk of frailty for mortality is described. Between the first follow-up (1995/1996) and 1 January 2000, 328 respondents died: 209 (63.7%) men and 119 (36.3%) women. The respondents who died were significantly older, had fewer years of education, and were more frequently unmarried and more disabled in 1995/1996. Women were more often frail than men. Of those who died, 39 percent fulfilled the criteria for static frailty, 35 percent for dynamic frailty and 23 percent met the criteria for both definitions of frailty. Static frailty was significantly associated with mortality in men and in women. Dynamic frailty was also associated with mortality in women but

it was not significantly associated with mortality in men. When disability and chronic diseases were included in the model as possible mediators, the effect of frailty slightly decreased.

In chapter 5, the endocrine and inflammatory risk factors for prevalent and incident frailty are reported. There are several reasons to expect that inflammatory and endocrine markers are associated with frailty but there is little empirical evidence yet. The aim of this study was to examine the associations between endocrine and inflammatory markers (serum concentrations of 25-hydroxyvitamin D (25(OH)D), interleukin-6 (IL-6), C-reactive protein (CRP), and insulin-like growth factor-1 (IGF-1)) and frailty, cross-sectionally and prospectively, i.e. the development of frailty in the subsequent three years. Inflammation is a response to different stimuli; pathogens, physical trauma and chemicals stimulate monocytes, macrophages and other cells to produce cytokines that induce the inflammation process. Aging is associated with an increased release of cytokines. Several of those cytokines such as C-reactive protein, and interleukin-6 (IL-6) are associated with functional decline and mortality. Interleukin-6 plays an important role in the acute inflammatory response and induces the production of hepatic acute- phase proteins such as C-reactive protein. Chronic inflammation is associated with chronic diseases such as cardiovascular diseases, rheumatoid arthritis, and diabetes mellitus but also with obesity. Inflammation has effect on endocrine system functioning. Chronic elevation of IL-6 has a negative effect on muscle mass and inhibits the production of growth hormone and insulin-like growth factor-1 (IGF-1). Growth hormone and IGF-1 play an important role in growth and development and maintenance of muscle mass in old age and IGF-1 serum levels decrease with age. Another endocrine marker is vitamin D. Vitamin D deficiency is also common in the elderly had has been associated with adverse outcomes of frailty such as falls and hip fractures. Vitamin D deficiency is associated with sarcopenia and decrease of muscle mass, which suggests an association with frailty but a direct association with frailty has not been examined. The relationship between the biological risk factors and frailty was examined at baseline (1995/1996) and the incidence of new frailty after three-years (1998/1999), excluding frail respondents at baseline. At baseline, 19 percent was frail and 14 percent became frail after three years of follow-up. Low 25(OH)D levels were strongly associated with

prevalent and incident frailty; moderately elevated levels of CRP were associated with incident frailty.

In chapter 6, the results of the qualitative study on the meaning of quality of life from the perspectives of older frail and non-frail persons are described. Quality of life is seldomly defined and the meaning of the concept for older community-dwelling adults has not been investigated frequently. During the analysis five themes emerged; (physical) health, psychological well-being, social contacts (with partner, family, friends and neighbors), activities (to enjoy, activities for social contacts, activities to relax, activities for health and activities to help others) and home & neighborhood. If health declines, other aspects became more important than health, especially social contact. Acceptance of health decline is very important for quality of life.

Furthermore, frailty is supposed to have a negative effect on quality of life but this has not been often examined yet. Most respondents (22 of 25) rated their quality of life satisfactory or good. Furthermore, it was examined whether these aspects differed between frail and non-frail persons. There were no differences between the frail persons and the non-frail persons, concerning the important aspects for quality of life. Quality of life decreases when frailty increases.

In chapter 7, the results of the qualitative study on the meaning of frailty and successful aging from the perspectives of older frail and non-frail persons are described. Few studies so far investigated the meaning of both terms from the perspective from older persons. These terms are often used to describe older persons. A frequently used definition of successful aging is that of Rowe and Kahn in which successful aging exists of three components; low probability of disease and disease-related disability and absence of risk factors for disease and disability, high cognitive and physical functional capacity, and active engagement with life.

Frailty meant to older persons a state characterized by reduced health, psychological problems such as being anxious and not feeling well, feeling down. Furthermore, it meant few social contacts and feelings of loneliness. It meant not being able to do things that the respondents liked to do. When the definitions of frailty described by the older persons were compared to existing definitions of frailty in the literature, it was found that the existing definitions mostly contain physical

components, while the concept also contained psychological and social aspects according to the respondents.

Successful aging was described as a process of growing older, in good health (physically and mentally), having a positive outlook, being active, and having social contacts. It meant being able to do the things the respondents liked to do. More respondents found themselves as aging successfully as would be according to the frequently used definition of successful aging of Rowe & Kahn.

The majority of the respondents (17 of 25) reported that they were aging successfully. Five respondents mentioned that they were frail and not aging successfully and three respondents were undecided.

Frailty and successful aging are related but different concepts. Frailty was a state characterized by health, psychological and social problems. Successful aging was the process of how a person aged. When health is maintained, older persons reported to aging successfully and reported that they felt not frail at all. When the respondent was less healthy, older persons reported to be partly frail but also partly successful.

In chapter 8, the main findings and conclusions are summarized and discussed with regard to methodological issues, and relevance for clinical practice. Furthermore, recommendations for further research are given.

The main findings of this thesis are the increased risk of frailty for adverse outcomes and the association between frailty and biological risk factors. Older frail persons have an increased risk for physical decline, institutionalization, and death. Furthermore, a low serum level of 25-hydroxyvitamin D (25(OH)D) was strongly associated with prevalent and incident frailty. In addition, moderately increased serum CRP was also associated with incident frailty. In this thesis we examined a static and dynamic definition of frailty and both definitions increased the risk for negative health consequences. Static frailty meant that a low level of functioning was related to adverse outcomes, which is not a new finding. However, dynamic frailty meant that decline in functioning in three or more areas of functioning, not always decline to the lowest level, also increased the risk for adverse outcomes. This has not been examined in other studies. Differences were found in the prevalence of frailty between men and women. Women were more often frail and suffered more

often from the negative health consequences of frailty. Older frail persons rated their quality of life on average lower than non-frail older persons. Despite of their frailty, most older person still rated their quality of life as satisfactory and most reported to age successfully.

Further research is needed to develop a sound definition of frailty. In this study, we have used the measurement instruments available in the LASA study. Our definition of static and dynamic frailty should be validated in other studies.

Moreover, any use of an instrument to measure frailty in health care practice, implies that the instrument should be short and easy measurable. The general practitioner or geriatrician might need the instrument to enable him or her by means of a few short questions or observations to determine whether the older person in his or her practice is frail, and start tailored interventions. This is especially important since recent studies have shown that interventions to prevent functional decline and disability are most effective when administered to moderately frail persons. Older persons with more advanced frailty benefited less from the interventions. Most frailty markers in this study were measured with validated questionnaires and several questionnaires had to be administered to determine the presence of the nine frailty markers. Further research is necessary to develop a short and easily applicable frailty instrument with the nine frailty markers that can be used in clinical practice.

Another recommendation for further research is to carry out studies, with short time intervals between the measurement cycles. In the LASA-study, the time between the intervals is three years, which is a very long period with regard to the development of frailty. Consequently, most frail persons who are frail at one measurement cycle will be not capable to participate in the next measurement cycle, they are most likely to be lost to follow-up. Shorter time intervals give more insight in the causes, pathway and risk factors of frailty. Especially short time intervals can give more insight in the biological risk factors and the devolvement of frailty.

In future studies, the connections between the three concepts quality of life, frailty and successful aging, should be further explored as these can show how older persons experience these concepts. It can provide additional information on how to improve quality of life, and prevent frailty with the perspective of successful aging.

Samenvatting

Samenvatting

Frailty of kwetsbaarheid komt steeds vaker voor bij ouderen. Omdat het aantal ouderen in Nederland toeneemt en de ouderen steeds ouder worden zal in de toekomst ook het aantal kwetsbare ouderen toenemen. Frailty of kwetsbaarheid is een relatief nieuw begrip dat vooral de laatste vijftien jaar steeds meer gebruikt wordt. Er is nog geen eenduidige definitie en daardoor varieert de gerapporteerde prevalentie van kwetsbaarheid bij ouderen tussen de zes en veertig procent, afhankelijk van de gehanteerde definitie. Los van de precieze definitie van kwetsbaarheid, gaat het bij kwetsbaarheid om problemen die ouderen in meerdere domeinen tegelijk hebben (lichamelijk, bijv. gewichtsverlies of inactief zijn, en psychologisch, bijv. een depressie), waardoor een negatieve spiraal kan ontstaan. Op dit moment is er nog weinig duidelijkheid over het ontstaan en verloop van kwetsbaarheid. Kwetsbaarheid is een toestand waarbij de oudere een hoog risico loopt op negatieve uitkomsten zoals vallen, hulpbehoevendheid, opname in verzorgings of verpleeghuis en sterfte als gevolg van verminderde fysiologische en psychologische reserves. Het gaat om een kwetsbaar evenwicht omdat de oudere nog maar weinig reserves heeft om verstoringen te kunnen opvangen en al bij een kleine verstoring uit zijn/haar evenwicht kan raken. Mogelijke oorzaken van kwetsbaarheid zijn veranderingen in het immuunsysteem, endocriene en neuro-musculaire veranderingen. Tot nu toe is naar de oorzaken nog weinig empirisch onderzoek verricht.

Hoewel kwetsbaarheid gezien wordt als een dynamische toestand met een hoge kans op negatieve consequenties, beperken de meeste studies zich tot nu toe tot statische definities (één moment van functioneren) van kwetsbaarheid.

In dit proefschrift is kwetsbaarheid gedefinieerd als de aanwezigheid van drie of meer scores boven de afkapwaarde van negen kwetsbaarheidkenmerken. De gekozen kwetsbaarheidkenmerken zijn laag lichaamsgewicht, matige longfunctie, verminderd cognitief functioneren, matig gezichtsvermogen, gehoorstoornis, incontinentie, weinig gevoel van controle (mastery), depressieve symptomen en lichamelijke inactiviteit.

Kwetsbaarheid wordt op een statische en dynamische manier gedefinieerd. De statische definitie houdt in slecht functioneren op één moment. De dynamische definitie houdt in verandering in functioneren tussen twee momenten.

De vraagstellingen van dit onderzoek zijn:

1) Wat is de relatie tussen kwetsbaarheid en negatieve gezondheidsuitkomsten: lichamelijke achteruitgang, opname in een verzorgings- of verpleeghuis en sterfte?
2) Wat is de relatie tussen endocriene en ontstekingsparameters en kwetsbaarheid?
3) Wat vinden oudere mensen die zelfstandig wonen belangrijk voor hun kwaliteit van leven?
4) Wat is de betekenis van kwetsbaarheid en succesvol ouder worden voor oudere mensen zelf?

Het onderzoek in dit proefschrift heeft plaatsgevonden binnen de Longitudinal Aging Study Amsterdam (LASA). LASA is een multidisciplinair cohort-onderzoek naar predictoren en consequenties van veranderingen in lichamelijk, cognitief, emotioneel en sociaal functioneren van ouderen. Het LASA-onderzoek is gestart in 1992/1993 met 3107 mannen en vrouwen in de leeftijd 55 tot 85 jaar, gestratificeerd naar leeftijd, geslacht en verwachte 5-jaarssterfte. Elke drie jaar vindt een dataverzameling plaats door middel van een hoofd- en een medisch interview. In dit proefschrift zijn gegevens gebruikt van de beginmeting en de tweede, derde en vierde meting van LASA. Bloedmonsters zijn afgenomen op de tweede meting in 1995/1996 bij alle personen die 65 jaar en ouder waren. Aanvullende informatie over visies op kwaliteit van leven, kwetsbaarheid en succesvol ouder worden bij kwetsbare en niet-kwetsbare ouderen is verzameld door middel van semi-gestructureerde interviews in 2004/2005 bij 25 thuiswonende ouderen.

In hoofdstuk 2 wordt de relatie tussen kwetsbaarheid en lichamelijke achteruitgang beschreven. Kwetsbaarheid is onderzocht met behulp van de statische en dynamische definitie. Lichamelijke achteruitgang is gedefinieerd als achteruitgang tussen 1995/1996 en 1998/1999. Lichamelijke achteruitgang is op twee manieren gemeten: door objectieve testen, de zogeheten ‘performance tests’ en op een meer

subjectieve wijze, door zelfgerapporteerde functionele beperkingen. Meetinstrumenten gebaseerd op tests en op zelfrapportage meten verschillende aspecten van lichamelijk functioneren. De samenhang tussen deze meetinstrumenten cross-sectioneel en longitudinaal is matig en daarom zijn deze beide meegenomen in het onderzoek. Bovendien is onderzocht of de gevolgen van kwetsbaarheid onafhankelijk zijn van de gevolgen van chronische ziekten.

Drieëntwintig procent van de deelnemers aan dit onderzoek ging gedurende drie jaar achteruit in objectief lichamelijk functioneren en vijfentwintig procent ging achteruit gemeten met de vragenlijst naar functionele beperkingen. Van degene die achteruitgingen in functioneren gemeten met de 'performance testen', voldeden 23% aan de criteria voor statische kwetsbaarheid, 26% aan de criteria voor dynamische kwetsbaarheid en 23% was kwetsbaar volgens beide definities. Met zelfgerapporteerde functionele beperkingen voldeed 34% aan de criteria voor statische kwetsbaarheid, 31 % aan de criteria voor dynamische kwetsbaarheid en 18% was kwetsbaar volgens beide definities. In dit onderzoek werd aangetoond dat statische kwetsbaarheid de kans op zelfgerapporteerde functionele beperkingen vergrootte. Verder vergrootte statische kwetsbaarheid de kans op achteruitgang met de 'performance tests' maar alleen voor de middeloudste groep ouderen. Dynamische kwetsbaarheid vergrootte de kans op gemeten lichamelijke achteruitgang alleen voor vrouwen en de kans op zelfgerapporteerde functionele beperkingen voor de totale steekproef. Deze effecten bleven aanwezig na correctie voor het aantal chronische ziekten.

In hoofdstuk 3 wordt de relatie tussen kwetsbaarheid op opname in een verzorgings- of verpleeghuis beschreven. Men neemt aan dat kwetsbaarheid de kans op opname vergroot maar tot nu toe is er weinig longitudinaal bewijs dat dit zo is. Ook heeft ieder land een ander zorgsysteem wat een vergelijking tussen onderzoek in de verschillende landen moeilijk maakt. Tot nu toe is vooral de kans op opname onderzocht bij groepen met een hoog risico voor opname zoals mensen met verminderd cognitief functioneren, of met een specifieke aandoening bijvoorbeeld de ziekte van Parkinson. Tijdens de onderzoeksperiode van 6 jaar werden er 104 vrouwen en 49 mannen opgenomen in een verzorgings- of verpleeghuis. Van deze personen voldeed 38% aan de definitie van statische kwetsbaarheid, 34% aan de definitie van dynamische kwetsbaarheid en 20% voldeed aan beide definities.

Degenen die werden opgenomen waren ouder en woonden vaker alleen, hadden meer chronische ziekten en meer functionele beperkingen. Er werd aangetoond dat statische en dynamische kwetsbaarheid de kans op opname vergrootte voor mannen en vrouwen. Deze effecten bleven aanwezig als rekening werd gehouden met het effect van chronische ziekten en functionele beperkingen.

In hoofdstuk 4 is het verband tussen kwetsbaarheid en de kans op sterfte beschreven. Vanaf de tweede meting van LASA (1995/1996) tot 1 januari 2000, zijn 328 respondenten overleden: 209 mannen en 119 vrouwen. De deelnemers die waren overleden waren ouder, lager opgeleid, vaker alleenstaand en hadden meer functionele beperkingen. In dit onderzoek waren er meer vrouwen kwetsbaar dan mannen. Van alle overledenen voldeed 39% aan de definitie voor statische kwetsbaarheid, 35 % aan die voor dynamische kwetsbaarheid en 23% was kwetsbaar volgens beide definities. Statische kwetsbaarheid verhoogde de kans om te overlijden voor zowel mannen als vrouwen. Dynamische kwetsbaarheid verhoogde de kans om te overlijden alleen voor vrouwen en niet voor mannen. Wanneer deze resultaten werden gecorrigeerd voor de effecten van chronische ziekten en functionele beperkingen, werd de kans om te sterven als gevolg van kwetsbaarheid iets kleiner maar bleef verhoogd.

In hoofdstuk 5 worden biologische risicofactoren voor het ontstaan van kwetsbaarheid en het verband van deze factoren met al aanwezige kwetsbaarheid onderzocht. In dit onderzoek zijn endocrinologische- en ontstekingsfactoren als risicofactor voor het ontstaan van kwetsbaarheid onderzocht. Er zijn verschillende redenen om aan te nemen dat biologische factoren kwetsbaarheid veroorzaken maar tot nu toe is er nog maar weinig empirisch bewijs. Het doel van dit onderzoek was na te gaan of er verband is tussen de endocrinologische factoren 25-hydroxyvitamine D (25(OH)D) en insulin-like growth factor-1 (IGF-1) en de ontstekingsfactoren Interleukine-6 (IL-6) en C-reactive protein (CRP) enerzijds en kwetsbaarheid anderzijds. Veroudering gaat gepaard met verhoging van ontstekingsfactoren zoals IL-6 en CRP. IL-6 speelt een belangrijke rol in de acute ontstekingsreactie en stimuleert de productie van acute-fase eiwitten zoals CRP in de lever. Chronische ontsteking is geassocieerd met chronische ziekten zoals hart- en vaatziekten, diabetes mellitus en obesitas. Ontstekingprocessen beïnvloeden het functioneren

van het endocriene systeem. Chronische verhoging van IL-6 heeft een negatieve invloed op spiermassa en vermindert de productie van groeihormoon en insulin-like growth factor-1. Groeihormoon en IGF-1 spelen een belangrijke rol in de groei, de ontwikkeling en het behoud van spiermassa op oudere leeftijd. Een andere endocriene marker is vitamine D. Een laag gehalte van vitamine D is geassocieerd met heupfracturen en sarcopenie (weinig spiermassa) en afname van de spierkracht. Een lage 25(OH)D spiegel wordt verondersteld samen te hangen met kwetsbaarheid maar deze samenhang is nog weinig onderzocht. Bestaande kwetsbaarheid werd gemeten in 1995/1996. Het ontstaan van nieuwe kwetsbaarheid werd gemeten tussen 1995/1996 en 1998/1999 waarbij de deelnemers die al kwetsbaar waren in 1995/1996 werden uitgesloten.

In 1995/1996 was 19% van de deelnemers kwetsbaar en na drie jaar was 14% kwetsbaar geworden. Een lage serumwaarde van 25-hydroxyvitamine D was een risicofactor voor het bestaan en het ontstaan van kwetsbaarheid. Een matig verhoogde serum-CRP waarde was ook een risicofactor voor het ontstaan van kwetsbaarheid.

In hoofdstuk 6 staan de resultaten van het kwalitatieve onderzoek naar de betekenis van kwaliteit van leven vanuit het perspectief van kwetsbare en niet-kwetsbare ouderen beschreven. Het concept kwaliteit van leven wordt zelden gedefinieerd en de betekenis van het concept voor ouderen zelf is tot nu toe weinig onderzocht. Verder wordt verondersteld dat kwetsbaarheid een negatief effect heeft op de kwaliteit van leven maar ook dit is weinig onderzocht.

In datgene wat de respondenten onder kwaliteit van leven verstonden waren vijf dimensies te onderscheiden: lichamelijke gezondheid, geestelijk welzijn, sociale contacten (met partner, familie, vrienden en buren), activiteiten (om gezond te blijven, om te ontspannen, sociale activiteiten, en activiteiten om anderen te helpen) en tot slot de woning en de omgeving. Naarmate de gezondheid afneemt worden andere aspecten belangrijker, zoals sociale contacten. De acceptatie van lichamelijke achteruitgang is erg belangrijk. Bijna alle respondenten (22) waren (zeer) tevreden over hun kwaliteit van leven. De overige drie deelnemers waren ontevreden over hun kwaliteit van leven.

Verder werd onderzocht of deze aspecten verschilden voor kwetsbare en niet-kwetsbare ouderen. Er waren geen verschillen tussen kwetsbare en niet-kwetsbare ouderen wat betreft de dimensies die belangrijk werden gevonden voor kwaliteit van leven, maar de kwaliteit van leven nam wel af als de kwetsbaarheid toenam.

In hoofdstuk 7 staan de resultaten van het kwalitatieve onderzoek naar de betekenis van de begrippen kwetsbaarheid en succesvol ouder worden vanuit het perspectief van de ouderen zelf beschreven. Tot op heden is er weinig onderzoek verricht wat deze begrippen betekenen voor ouderen zelf terwijl de begrippen vaak gebruikt worden om ouderen te omschrijven. Een veel gebruikte definitie voor succesvol ouder worden is de definitie van Rowe& Kahn die bestaat uit 3 criteria waarin je moet voldoen om succesvol ouder te worden; kleine kans op ziekte & beperkingen door ziekte en de afwezigheid van risicofactoren voor ziekte & beperkingen, goed lichamelijk en cognitief functioneren, actieve deelname aan het leven. Kwetsbaarheid betekende voor de ouderen zelf een toestand van verminderde gezondheid, psychologische klachten zoals angst en niet lekker in zijn/haar vel zitten, zich depressief voelen, verminderde sociale contacten en eenzaamheid. Het kwam erop neer dat men niet kan doen wat men wilt.

Succesvol ouder worden is volgens de ouderen een proces, een situatie waarin men in goede gezondheid verkeert (lichamelijk en geestelijk), optimistisch is, positief in het leven staat, erg actief is, en vele sociale contacten heeft. Kortom, dat men kan doen wat men graag wil doen. De meerderheid van de respondenten (17 van de 25) gaven aan zelf succesvol ouder te worden. Vijf respondenten vonden dat zij kwetsbaar waren en niet succesvol ouder werden en drie respondenten vonden beide begrippen van toepassing. Wanneer de betekenis van deze begrippen werd vergeleken met bestaande definities en criteria voor deze begrippen, viel op dat kwetsbaarheid volgens de ouderen zelf breder is dan de bestaande definities, welke voornamelijk lichamelijke kenmerken omvatten. Voor het begrip succesvol ouder worden kwam de definitie van de respondenten overeen met een veel gebruikte definitie van succesvol ouder worden, afkomstig van Rowe & Kahn. Echter meer mensen vonden van zichzelf dat ze succesvol ouder werden dan het aantal die volgens de definitie van Rowe & Kahn succesvol ouder zou worden.

Kwetsbaarheid en succesvol ouder zijn begrippen die samenhangen. Kwetsbaarheid is een toestand die gekaraktiseerd wordt door

gezondheidsproblemen, psychologische en sociale problemen. Succesvol ouder worden werd beschreven als het proces van ouder worden. Wanneer de gezondheid goed bleef, gaven mensen aan succesvol ouder te worden en zichzelf niet kwetsbaar te vinden. Wanneer de gezondheid minder is, gaven mensen aan zichzelf voor een deel kwetsbaar te vinden en ook voor een deel succesvol.

In hoofdstuk 8 staan de belangrijkste resultaten en conclusies beschreven en worden deze bediscussieerd. Ook worden aanbevelingen gedaan voor verder onderzoek.

De belangrijkste bevindingen uit dit proefschrift zijn dat kwetsbaarheid de kans op negatieve gezondheidsuitkomsten vergroot en dat kwetsbaarheid samenhangt met enkele biologische risicofactoren. Ouderen die kwetsbaar zijn, hebben meer kans op lichamelijke achteruitgang, opname in een verzorgings- of verpleeghuis en om te overlijden. Verder bleek een lage 25-hydroxy vitamine D spiegel sterk samen te hangen met kwetsbaarheid. Ook matige verhoging van de ontstekingsfactor CRP is een risicofactor voor het ontstaan van kwetsbaarheid. Zowel een statische definitie als een dynamische definitie van kwetsbaarheid zijn beschouwd, waarbij bleek dat beide definities samenhangen met de negatieve consequenties van kwetsbaarheid. Dit geeft aan dat slecht functioneren op één moment maar ook dat achteruitgang in functioneren in drie of meer domeinen leidt tot negatieve gevolgen. Ouderen die achteruitgang ervoeren in drie of meer domeinen van functioneren maar die lang niet altijd al op een laag niveau functioneerden, hebben een verhoogde kans op de negatieve gevolgen van kwetsbaarheid. Er bleken wel verschillen te zijn tussen mannen en vrouwen met betrekking tot kwetsbaarheid. Vrouwen waren vaker kwetsbaar en zij ondervonden vaker de gevolgen van kwetsbaarheid. Ouderen die kwetsbaar waren ervoeren gemiddeld een lagere kwaliteit van leven. Maar ondanks de kwetsbaarheid ervoeren de meeste ouderen in dit onderzoek hun kwaliteit van leven toch nog als voldoende tot goed.

Verder onderzoek zou moeten plaatsvinden naar de definitie en meting van kwetsbaarheid. In dit onderzoek hebben we gebruik gemaakt van de binnen LASA beschikbare meetinstrumenten. Onze definitie van dynamische en statische kwetsbaarheid zal moeten worden getest in andere populaties om meer inzicht te geven in de validiteit van deze definitie.

Echter om een meetinstrument voor kwetsbaarheid in de gezondheidszorg te kunnen gebruiken, zal het eenvoudig en makkelijk hanteerbaar moeten zijn. De huisarts of geriater zal door middel van een aantal korte vragen of observaties willen bepalen wie kwetsbaar is en wie niet, om zo gericht hulp te kunnen bieden aan de oudere met veel verschillende gezondheidsproblemen. Eerder onderzoek al heeft aangetoond dat interventies alleen in een vroeg stadium van kwetsbaarheid effectief zijn in het voorkomen/uitstellen van verdere achteruitgang in functioneren. De meeste kwetsbaarheidkenmerken in dit onderzoek zijn afgeleid van vragenlijsten en voor de bepaling van kwetsbaarheid moeten negen gebieden worden nagevraagd/gemeten. Verder onderzoek zal moeten plaatsvinden om een manier te ontwikkelen waarop deze kwetsbaarheidmarkers gemeten kunnen worden door middel van korte, simpele vragen waardoor het mogelijk wordt om kwetsbaarheid in de dagelijkse gezondheidszorgpraktijk te kunnen meten.

Een belangrijke aanbeveling voor verder onderzoek naar dynamische kwetsbaarheid is de tijd tussen verschillende meetrondes te verkorten. In het LASA-onderzoek is de periode tussen de meetmomenten drie jaar en dit is een erg lange periode voor kwetsbare ouderen. Kwetsbaarheid kan tot gevolg hebben dat men bij de volgende meetronde niet meer in staat is om deel te nemen aan het onderzoek. Dit maakt het verloop van kwetsbaarheid niet inzichtelijk. Kortere tijdsintervallen tussen de verschillende meetrondes kan het inzicht vergroten in het ontstaan en verloop van kwetsbaarheid, en de samenhang met (biologische) risicofactoren.

In vervolgonderzoek zou het verband tussen de concepten kwaliteit van leven, succesvol ouder worden en kwetsbaarheid moeten worden bestudeerd hoe volgens ouderen deze begrippen samenhangen. Dit kan meer informatie opleveren hoe de kwaliteit van leven, het proces van succesvol ouderen worden kan worden verbeterd en welke mogelijkheden er zijn om kwetsbaarheid te beïnvloeden.

Dankwoord

Dankwoord

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About the author

Martine Puts was born in Amsterdam on the 9th of February 1977. She graduated from secondary school Huygenwaard (pre-university education) in 1995. She started with nursing training at the Hogeschool Amsterdam in 1995 where she graduated with a bachelor degree in 1999. She subsequently studied Health Sciences at the University Maastricht. She graduated in November 2001 with a major in Health Care Studies. Martine worked part-time at a home care organization and a hospital during her studies. In December 2001, Martine became a PhD student in the Longitudinal Aging study Amsterdam at the Institute for Research in Extramural Medicine (EMGO-Institute), VU University Medical Center, Amsterdam. Her study focused on frailty, the results of which are presented in this thesis. She has followed methodological and statistical courses of the Postgraduate Epidemiology program of the EMGO Institute and Netherlands School of Primary Care Research during the PhD project. Since September 2004, she is registered as a Master of Science in Epidemiology with the Netherlands Epidemiology Society.
Martine worked since September 2005 as a researcher on the project “Time trends in disability and chronic diseases” together with prof.dr. D. Deeg (VUmc), dr. F. Schellevis (NIVEL), dr. N. Hoeymans (RIVM) and dr. W. Nusselder (Erasmus MC). Martine hopes to start working as a postdoc in April 2006 in the Center for Clinical Epidemiology and Community Studies of the Lady Davis Institute for Medical Research of the Jewish General Hospital with professor H. Bergman and professor C. Wolfson in Montreal, Quebec, Canada.

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